

# BMJ Open

## Weight change patterns and subsequent onset of type 2 diabetes mellitus in urban and rural Japan

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014684
Article Type:	Research
Date Submitted by the Author:	11-Oct-2016
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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Health services research, Epidemiology, Nutrition and metabolism, Sports and exercise medicine
Keywords:	weight change, type 2 diabetes, body mass index, Asian, weight cycling

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3 1 **Weight change patterns and subsequent onset of type 2 diabetes mellitus in**  
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5 2 **urban and rural Japan**

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39 17 **Keywords:** weight change, type 2 diabetes, body mass index, Asian, weight cycling  
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44 19 **Word count: 2,718**  
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3 **ABSTRACT**

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6 **Objective:** To investigate how weight change patterns impact the risk of diabetes, including  
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9 weight change since 20 years of age.

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12 **Design:** Cohort study.

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15 **Setting:** Primary healthcare, urban and rural Japan.

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18 **Participants:** 20,708 urban and 9,670 rural residents.

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22 **Primary outcome measure:** Odds ratios (ORs) for diabetes in weight loss, loss–gain, stable,  
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24 gain–loss and weight gain groups for 10 years. Weight gain and loss were defined as more  
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27 than  $\pm 4\%$  change from baseline weight.

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31 **Results:** In the urban region, the ORs relative to the stable group for the loss–gain and gain–  
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33 loss groups were 0.63 (95% CI: 0.45–0.89) and 0.51 (95%CI: 0.32–0.82) for men and 0.72  
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35 (95%CI: 0.39–1.34) and 1.05 (95%CI: 0.57–1.95) for women, respectively, whereas in the  
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37 rural region, they were 1.58 (95%CI: 0.78–3.17) and 0.44 (95%CI: 0.15–1.29) in men and  
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39 0.41 (95%CI: 0.12–1.44) and 0.77 (95%CI: 0.28–2.14) in women, respectively. The ORs for  
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41 an increase in weight of 5–10 kg since the age of 20 years were 1.54 (95%CI: 1.03–2.30) in  
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43 men and 0.96 (95%CI: 0.55–1.65) in women.

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46 **Conclusions:** Data from Japanese urban residents suggest that weight cycling reduces the  
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48 risk of diabetes. These results differ from those in Western studies, perhaps owing to the  
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50 motivations underlying the weight cycling.

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3 43 **Strengths and limitations of this study**

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6 44 ● In urban Japan, weight cyclers have a similar or lower risk of diabetes than people who  
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9 45 maintain a constant body weight.
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11 46 ● In urban and rural Japan, sustained weight gain increases the risk of diabetes.
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13 47 ● There is a dose–response relationship in both sexes between weight gain since the age of  
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15 48 20 years and the risk of diabetes.
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17 49 ● Odds ratios may change according to the threshold of  $\pm 4\%$  weight change in 10 years.
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19 50 ● Levels of insulin secretion and sensitivity were not measured.
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3 **52 INTRODUCTION**

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6 53 Weight gain is a well-known risk factor for incidental type 2 diabetes. Research in people of  
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9 54 Western, Oriental and African descent has quantitatively established the risks of developing  
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11 55 diabetes in relation to increases and decreases in weight.[1-3] Two major studies in the USA,  
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13 56 the Framingham Heart Study and the National Health and Nutrition Examination Survey,  
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15 57 have both reported that weight cyclers, people who repeatedly gain and lose weight over  
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17 58 short periods, can be at an increased risk of diabetes.[4, 5] However, the risk of diabetes in  
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19 59 Asian weight cyclers remains to be established.  
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23 60 Because of the preconception that links being slim to an aesthetic standard,[6, 7] many  
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25 61 Asian women make efforts to lose weight.[8, 9] Another group likely to try to reduce weight  
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27 62 are middle-aged East Asian businesspeople who have gained weight but have few  
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29 63 opportunities for physical activity. Recent studies have demonstrated that East Asians are  
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31 64 much more likely than Westerners to develop type 2 diabetes at a lower body mass index  
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33 65 (BMI).[10] As a result, it may take only a small change in weight to alter the risk of diabetes  
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35 66 of East Asians. The aim of this study was to establish whether weight cyclers residing in  
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37 67 Japan were at an increased risk of diabetes. We used Japanese urban and rural data to  
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39 68 examine this clinical question in populations with various lifestyles.  
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46 **70 METHODS**

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48 **71 Study participants and measurements**

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52 72 In this cohort study, we enrolled participants from an urban area, Tokyo Metropolis, and a  
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54 73 rural area, Yamanashi Prefecture. In Tokyo, we enrolled employees of private companies who  
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56 74 underwent medical check-ups between January 2005 and December 2014 at St. Luke's  
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3 75 International Hospital. These annual medical check-ups were based on a legal obligation  
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5 76 imposed by the Industrial Safety and Health Act in Japan.[11] In Yamanashi Prefecture, we  
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7 77 enrolled employees and residents who paid for a private comprehensive medical check-up  
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9 78 service between April 1999 and March 2009 at the Yamanashi Koseiren Health Care Center.  
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11 79 A subset of participants in Yamanashi used a subsidy from their employing companies or  
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13 80 administrative agencies to receive the private medical check-up. Thus, data sets covering a  
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15 81 10-year period in two institutions were used in the research. Inclusion criteria included no  
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17 82 diagnosis of diabetes and HbA1c less than 6.5% (48 mmol/mol) during a baseline period for  
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19 83 the first 3 years of the 10-year period. Those included were also required to undergo a  
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21 84 medical check-up at least twice during the outcome measurement period of the later seven  
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23 85 years of the study. The onset of diabetes was identified through questionnaires for the  
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25 86 diagnosis of diabetes, the commencement of diabetic therapies or glycated haemoglobin  
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27 87 (HbA1c)  $\geq$  6.5% (48 mmol/mol).[12, 13] In the institution in Tokyo, trained nurses  
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29 88 interviewed the participants from the age of 20 years to establish their changes in weight.  
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31 89 BMI was calculated as the participant's weight in kilograms divided by the square of their  
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33 90 height in metres.  
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### 42 **Weight change categories**

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45 93 The participants were categorised into five groups according to their histories of weight  
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47 94 change during the 3–10 years since the baseline period. The stable group comprised the  
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49 95 participants whose weight had not changed from baseline by more than  $\pm$ 4%. The sustained  
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51 96 gain group were the participants who gained more than 4% of their baseline weight and did  
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53 97 not subsequently lose this extra weight. Similarly, the sustained loss group were the  
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55 98 participants who lost more than 4% of their baseline weight and did not subsequently regain  
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3 99 this weight. The gain–loss group included the participants who gained more than 4% of their  
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5 100 baseline weight but brought their weight back below +4%. The loss–gain group were the  
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7 101 participants who lost more than 4% of their baseline weight but brought their weight back  
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10 102 above –4%.

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13 103 The  $\pm 4\%$  change of weight used for this categorisation was determined as approximately a  
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15 104 one-unit change for a person with a BMI of  $22 \text{ kg/m}^2$ . This was based on the 2014 reference  
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17 105 mean BMIs for Japanese men and women of  $23.6 \text{ kg/m}^2$  and  $21.7 \text{ kg/m}^2$ , respectively.[14] It  
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19 106 also took into consideration the relatively short time period of ten years for observation. The  
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21 107 gain–loss and loss–gain group participants were the weight cyclers of interest.  
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### 26 27 109 **Statistical analysis**

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31 110 The baseline characteristics recorded for the participants were age, weight, height, BMI,  
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33 111 HbA1c and fasting plasma glucose. The incidence of diabetes was measured after the  
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35 112 participants were categorised, and any data measured after a diagnosis of diabetes were  
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37 113 ignored to conserve temporality of exposure to outcome for an epidemiological  
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39 114 causation.[15] We used univariate and multivariate logistic regressions to compare the risk of  
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41 115 diabetes between the categorised groups. In the urban data of Tokyo Metropolis, covariates  
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43 116 used for adjustment at baseline were age, weight change from 20 years of age, BMI, smoking  
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45 117 habits, alcohol consumption and physical activity. In the rural data of Yamanashi Prefecture,  
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47 118 the available covariates for adjustment at baseline were age, BMI, smoking habit and alcohol  
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49 119 consumption. The analyses were stratified by sex. All statistical analyses were performed  
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51 120 using SAS statistical software (version 9.3, SAS Institute, NC, USA). The descriptive  
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53 121 statistics are reported as means and standard deviations (SD). All reported p values were  
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55 122 2-sided; *P* values of  $<0.05$  were considered statistically significant.  
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## 124 RESULTS

### 125 Participants

126 For the multivariate analyses of primary interest, 10,094 men and 10,614 women were  
 127 enrolled from Tokyo Metropolis (table 1). The means (SDs) of the baseline characteristics for  
 128 the men in the urban region were as follows: age 49.6 (11.9) years, weight 68.8 (9.7) kg, BMI  
 129 23.7 (2.8) kg/m<sup>2</sup> and HbA1c 5.4% (0.3%) [35.3 (3.7) mmol/mol]. For the women in the urban  
 130 region, these values were as follows: age 48.3 (11.3) years, weight 52.3 (7.4) kg, BMI 21.0  
 131 (2.9) kg/m<sup>2</sup> and HbA1c 5.3% (0.4%) [35.0 (3.8) mmol/mol].

132 Table 1 also shows the baseline characteristics of 4,818 men and 4,852 women enrolled  
 133 from Yamanashi Prefecture. The baseline characteristics for the men in the rural region were  
 134 as follows: age 51.2 (10.3) years, weight 65.7 (9.1) kg, BMI 23.2 (2.7) kg/m<sup>2</sup> and HbA1c  
 135 5.3% (0.3%) [34.3 (3.8) mmol/L]. For the women in the rural area, the values were as  
 136 follows: age 52.1 (9.4) years, weight 53.1 (7.5) kg, BMI 22.1 (2.9) kg/m<sup>2</sup> and HbA1c 5.3%  
 137 (0.3%) [34.4 (3.5) mmol/L].

138 **Table 1. Baseline characteristics of the participants from urban (Tokyo Metropolis) and**  
 139 **rural (Yamanashi Prefecture) regions of Japan.**

Characteristics, mean (standard deviation)	Men	Women
<b>Urban region</b>		
No.	10,094	10,614
Age, years	49.6 (11.9)	48.3 (11.3)
Weight, kg	68.8 (9.7)	52.3 (7.4)
Height, cm	170.4 (6.1)	157.7 (5.6)
Body mass index, kg/m <sup>2</sup>	23.7 (2.8)	21.0 (2.9)
HbA1c, %	5.4 (0.3)	5.3 (0.4)



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(HbA1c, mmol/mol)	35.3 (3.7)	35.0 (3.8)
Fasting plasma glucose, mg/dL	100.8 (8.6)	94.5 (8.0)
(Fasting plasma glucose, mmol/L)	5.6 (0.5)	5.2 (0.4)

9 **Rural region**

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No.	4,818	4,852
Age, years	51.2 (10.3)	52.1 (9.4)
Weight, kg	65.7 (9.1)	53.1 (7.5)
Height, cm	168.1 (6.2)	154.8 (5.6)
Body mass index, kg/m <sup>2</sup>	23.2 (2.7)	22.1 (2.9)
HbA1c, %	5.3 (0.3)	5.3 (0.3)
(HbA1c, mmol/mol)	34.3 (3.8)	34.4 (3.5)
Fasting plasma glucose, mg/dL	96.3 (9.0)	93.2 (8.5)
(Fasting plasma glucose, mmol/L)	5.3 (0.5)	5.2 (0.5)

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141 **Risk of diabetes in urban and rural Japan**

142 Tables 2 and 3 present the incidence of diabetes and the odds ratios (ORs) for each  
143 explanatory variable in the urban and rural regions, respectively. For the men in the urban  
144 region, the adjusted ORs (95% confidence intervals [95% CIs]) compared to the stable group  
145 were 3.07 (2.15–4.39) in the sustained gain group, 0.51 (0.32–0.82) in the gain–loss group,  
146 0.63 (0.45–0.89) in the loss–gain group and 1.11 (0.77–1.59) in the sustained loss group. For  
147 the women in the urban region, the adjusted ORs relative to the stable group were 7.00 (4.11–  
148 11.94) in the sustained gain group, 1.05 (0.57–1.95) in the gain–loss group, 0.72 (0.39–1.34)  
149 in the loss–gain group and 1.48 (0.80–2.74) in the sustained loss group. For the men in the  
150 rural region, the adjusted ORs were 3.15 (1.70–5.83) in the sustained gain group, 0.44 (0.15–  
151 1.29) in the gain–loss group, 1.58 (0.78–3.17) in the loss–gain group and 0.36 (0.12–1.05) in  
152 the sustained loss group. For the women in the rural region, the adjusted ORs were 1.43

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153 (0.59–3.48) in the sustained gain group, 0.77 (0.28–2.14) in the gain–loss group, 0.41 (0.12–  
 154 1.44) in the loss–gain group and 0.32 (0.09–1.10) in the sustained loss group.

155 **Table 2. Incidence of diabetes mellitus (DM) over 10 years in an urban region of Japan**  
 156 **and odds ratios related to patterns of weight change and other variables**

Exposure variables		Acquired DM / No. of subjects (incidence, %)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Men (No. For multivariate analysis =10,094)</b>				
Baseline age	Per 10 years	—	1.44 (1.33–1.55)	1.44 (1.29–1.61)
Weight change from 20 years of age, kg	< –5	7/1438 (0.5)	2.18 (1.14–4.18)	1.68 (0.75–3.80)
	–5 to +5	73/10646 (0.7)	Ref	Ref
	+5 to +10	31/3200 (1.0)	1.98 (1.45–2.72)	1.54 (1.03–2.30)
	> +10	78/2166 (3.6)	3.37 (2.54–4.48)	2.08 (1.40–3.10)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	6/387 (1.6)	1.35 (0.57–3.16)	0.88 (0.29–2.70)
	18.5–22	49/4236 (1.2)	Ref	Ref
	22–25	168/7220 (2.3)	2.04 (1.48–2.89)	1.73 (1.14–2.63)
	> 25	190/4699 (4.0)	3.60 (2.62–4.94)	2.52 (1.60–3.95)
Weight change pattern over 10 years	Sustained loss	66/1903 (3.5)	1.39 (1.03–1.87)	1.11 (0.77–1.59)
	Loss–gain	87/4644 (1.9)	0.74 (0.56–0.97)	0.63 (0.45–0.89)
	Stable	142/5621 (2.5)	Ref	Ref
	Gain–loss	38/3063 (1.2)	0.49 (0.34–0.70)	0.51 (0.32–0.82)
	Sustained gain	80/1311 (6.1)	2.51 (1.89–3.32)	3.07 (2.15–4.39)
Smoking	None	123/6385 (1.9)	Ref	Ref
	Ex-smoker	150/5940 (2.5)	1.32 (1.04–1.68)	0.97 (0.71–1.31)
	Current smoker	140/4217 (3.3)	1.75 (1.37–2.23)	1.73 (1.25–2.34)
Alcohol drinking	None	69/2250 (3.1)	Ref	Ref
	Sometimes	48/1667 (2.9)	0.94 (0.65–1.36)	0.96 (0.66–1.40)
	Usually	156/6177 (2.5)	0.82 (0.61–1.09)	0.78 (0.58–1.05)
Duration of walking per day	Per 30 min	—	0.996 (0.92– 1.08)	1.01 (0.92–1.11)
Physical activity	0–1/week	85/3282 (2.6)	Ref	Ref

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	1–2/week	108/4105 (2.6)	1.02 (0.76–1.36)	1.02 (0.76–1.36)
	3–5/week	43/1541 (2.8)	1.08 (0.74–1.57)	0.98 (0.67–1.45)
	6–7/week	37/1166 (3.2)	1.23 (0.83–1.82)	1.06 (0.69–1.62)
<b>Women (No. for multivariate analysis = 10,614)</b>				
Baseline age	Per 10 years	—	1.66 (1.48–1.87)	1.78 (1.50–2.12)
Weight change from 20 years of age, kg	< –5	11/439 (2.5)	0.71 (0.33–1.54)	0.48 (0.18–1.25)
	–5 to +5	61/5243 (1.2)	Ref	Ref
	+5 to +10	109/4779 (2.3)	1.42 (0.93–2.16)	0.96 (0.55–1.65)
	> +10	232/6081 (3.8)	5.41 (3.92–7.47)	2.10 (1.20–3.67)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	20/2916 (0.7)	1.24 (0.74–2.08)	1.47 (0.76–2.86)
	18.5–22	52/9388 (0.6)	Ref	Ref
	22–25	60/3676 (1.6)	2.98 (2.05–4.33)	2.01 (1.21–3.34)
	> 25	57/1470 (3.9)	7.24 (4.95–10.59)	2.91 (1.53–5.52)
Weight change pattern over 10 years	Sustained loss	24/1661 (1.4)	2.11 (1.25–3.54)	1.48 (0.80–2.74)
	Loss–gain	32/4022 (0.7)	1.15 (0.72–1.86)	0.72 (0.39–1.34)
	Stable	36/5212 (1.3)	Ref	Ref
	Gain–loss	30/4630 (0.6)	0.94 (0.58–1.53)	1.05 (0.57–1.95)
	Sustained gain	67/1925 (3.5)	5.19 (3.45–7.80)	7.00 (4.11–11.94)
Smoking	None	156/14,194 (1.1)	Ref	Ref
	Ex-smoker	17/1789 (1.0)	0.86 (0.52–1.143)	0.85 (0.45–1.61)
	Current smoker	16/1467 (1.1)	0.99 (0.59–1.67)	1.20 (0.63–2.32)
Alcohol drinking	None	78/5669 (1.4)	Ref	Ref
	Sometimes	20/2035 (1.0)	0.71 (0.43–1.17)	0.91 (0.55–1.52)
	Usually	27/2910 (0.9)	0.67 (0.43–1.04)	0.95 (0.60–1.51)
Duration of walking per day	Per 30 min	—	1.01 (0.93–1.11)	1.01 (0.90–1.13)
Physical activity	0–1/week	37/3894 (1.0)	Ref	Ref
	1–2/week	42/3760 (1.1)	1.18 (0.76–1.84)	1.11 (0.70–1.75)
	3–5/week	27/1874 (1.4)	1.52 (0.93–2.52)	1.14 (0.67–1.94)
	6–7/week	19/1086 (1.7)	1.86 (1.06–3.24)	1.43 (0.79–2.60)

157 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

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159 **Table 3. Incidence of diabetes mellitus (DM) over 10 years in a rural region of Japan**  
 160 **and odds ratios related to patterns of weight change and other variables**

Exposure variables		Acquired DM / No. of subjects (incidence, %)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Men (No. for multivariate analysis = 4818)</b>				
Baseline age	Per 10 years	—	1.36 (1.08–1.72)	1.60 (1.24–2.05)
	< 18.5	0/167 (0)	—	—
Baseline BMI, kg/m <sup>2</sup>	18.5–22	10/1425 (0.7)	Ref	Ref
	22–25	21/2079 (1.0)	1.44 (0.68–3.08)	1.69 (0.79–3.63)
	> 25	35/1148 (3.1)	4.45 (2.19–9.03)	5.81 (2.82–11.97)
Weight change pattern over 10 years	Sustained loss	4/725 (0.6)	0.43 (0.15–1.25)	0.36 (0.12–1.05)
	Loss–gain	13/681 (1.9)	1.50 (0.75–3.00)	1.58 (0.78–3.17)
	Stable	22/1719 (1.3)	Ref	Ref
	Gain–loss	4/916 (0.4)	0.34 (0.12–0.99)	0.44 (0.15–1.29)
	Sustained gain	23/778 (3.0)	2.35 (1.30–4.24)	3.15 (1.70–5.83)
Smoking	None	23/1695 (1.4)	Ref	Ref
	Ex-smoker	8/998 (0.8)	0.59 (0.26–1.32)	0.72 (0.32–1.64)
	Current smoker	35/2126 (1.7)	1.22 (0.72–2.07)	1.50 (0.85–2.62)
Drinking	None	11/1071 (1.0)	Ref	Ref
	Drinker	55/3748 (1.5)	1.44 (0.75–2.75)	1.52 (0.79–2.94)
<b>Women (No. for multivariate analysis = 4852)</b>				
Baseline age	Per 10 years	—	1.43 (0.99–2.06)	1.23 (0.83–1.84)
	< 18.5	0/411 (0)	—	—
Baseline BMI, kg/m <sup>2</sup>	18.5–22	7/2135 (0.3)	Ref	Ref
	22–25	14/1563 (0.9)	2.75 (1.11–6.82)	2.69 (1.07–6.75)
	> 25	13/744 (1.8)	5.41 (2.15– 13.60)	5.29 (2.07–13.51)
Weight change pattern over 10 years	Sustained loss	3/863 (0.3)	0.37 (0.11–1.29)	0.32 (0.09–1.10)
	Loss–gain	3/757 (0.4)	0.42 (0.12–1.47)	0.41 (0.12–1.44)
	Stable	15/1615 (0.9)	Ref	Ref
	Gain–loss	5/827 (0.6)	0.65 (0.24–1.79)	0.77 (0.28–2.14)
	Sustained gain	8/791 (1.0)	1.09 (0.46–2.58)	1.43 (0.59–3.48)
Smoking	None	2/646 (0.3)	Ref	Ref

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	Ex-smoker	29/3822 (0.8)	2.45 (0.58–10.31)	2.19 (0.52–9.26)
	Current smoker	3/375 (0.8)	2.60 (0.43–15.60)	3.33 (0.55–20.28)
Drinking	None	31/3542 (0.9)	Ref	Ref
	Drinker	3/1311 (0.2)	0.26 (0.08–0.85)	0.29 (0.09–0.95)

161 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

162

## 163 DISCUSSION

164 The data for the urban region suggest that the risk of diabetes in male and female weight  
 165 cyclers was similar to or lower than that in the participants who maintained a stable weight.  
 166 In particular, the data for Japanese men residing in an urban region indicate that, compared  
 167 with the men who maintained a stable weight, there was a significantly reduced risk of  
 168 diabetes with weight cycling. The data for Japanese women residing in a rural region also  
 169 suggest a reduced risk of diabetes with weight cycling compared with maintaining a stable  
 170 weight.

171 These findings are not consistent with those from previous studies of Western populations,  
 172 which showed that weight cycling increased the risk of diabetes. In the Framingham Heart  
 173 Study, approximately 1 kg/m<sup>2</sup> of weight cycling in American men and women aged between  
 174 40 and 50 years carried a hazard ratio of 1.1 (95%CI: 0.8–1.5) for the risk of diabetes after  
 175 adjustment for sex and BMI at 25 years of age.[4] In an American study of middle-aged  
 176 women (the National Health and Nutrition Examination Survey), weight cycling of 4.5–9.1  
 177 kg and 9.1–22.2 kg with an intentional loss of weight three or more times in four years  
 178 carried ORs for the risk of diabetes of 1.11 (95%CI: 0.89–1.37) and 1.39 (95%CI: 0.90–2.13),  
 179 respectively.[5] A study from a cohort of medical students at the Johns Hopkins University  
 180 School of Medicine reported that the highest quartile of BMI variability at ages between 25

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3 181 and 45 years had an OR of 2.1 (95%CI: 1.0–4.6) for the risk of diabetes after 50 years,  
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5 182 compared with the other three lower quartiles.[16]  
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9 183 Inconsistency between the Western studies and this study that weight cycling was not  
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11 184 associated with an increase in the risk of diabetes but may even reduce the risk, may be due  
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13 185 to ethnic differences in diet,[17] the capacity to gain weight[18] and self-consciousness about  
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15 186 body weight.[19] Further research is needed to explore why the relationship between weight  
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17 187 cycling and risk of diabetes is reversed between Western and East Asian populations. The  
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19 188 reason may be attributable to different motivations to lose weight in the context of different  
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21 189 diet cultures and body self-consciousness.[20] The East Asians who try to lose weight are  
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23 190 particularly those who are relatively concerned about the poor health outcomes of being  
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25 191 overweight. Westerners in the study cohorts described who tried to lose weight may, in an  
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27 192 extreme expression, have been those who lost and regained a great deal of weight and  
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29 193 potentially ran the risk of poor health outcomes.  
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34 194 From the data from the urban region, a weight increase of more than +5 kg above the  
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36 195 participant's weight at the age of 20 years increased the risk of developing diabetes with a  
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38 196 dose–response relationship in both men and women (table 2). Furthermore, in both sexes, an  
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40 197 increase in weight of more than +10 kg above that when aged 20 years more than doubles the  
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42 198 risk of diabetes, with statistical significance, compared to the risk for those who maintained  
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44 199 their weight within  $\pm 5$  kg of their weight when aged 20 years. These results agree with the  
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46 200 study in a US cohort, which reported a relative risk of 3.2 (95%CI: 1.4–7.4) for the highest  
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48 201 quartile of BMI increase from 25 to 45 years of age in comparison with the other three lower  
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50 202 quartiles.[16] A dose–response relationship involving weight change from that aged 20 years  
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52 203 occurred in the Japanese women residing in the urban region, with ORs of 0.48 (95%CI:  
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54 204 0.18–1.25) for a change less than 5 kg, 0.96 (95%CI: 0.55–1.65) for an increase of between 5  
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3 205 and 10 kg and 2.10 (95%CI: 1.20–3.67) for an increase greater than 10 kg. In contrast, the  
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5 206 Japanese men who had lost 5 kg or more of weight between the age of 20 years and early  
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7 207 middle age had an OR of 1.68 (95%CI: 0.75–3.80). This paradoxically increased OR was  
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10 208 probably due to the small number of participants (seven) who developed diabetes among a  
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12 209 weight loss group of 1438 people.

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15 210 This study had several limitations. The first of these was the threshold of  $\pm 4\%$  weight  
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17 211 change in 10 years. This threshold referred to a study from United Kingdom on the  
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19 212 association between weight change and the risk of diabetes.[21] The threshold of  $\pm 4\%$  weight  
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21 213 change was calculated as approximately 1 BMI unit in Japanese people with a mean BMI of  
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23 214  $23 \text{ kg/m}^2$ . However, the threshold for categorisation of weight cycling should vary according  
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25 215 to mean BMIs in different ethnicities, in which people have different insulin sensitivities.[10,  
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27 216 22] Second, we did not evaluate insulin sensitivity. Measuring fasting plasma glucose and  
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29 217 insulin concentration to calculate HOMA-IR,[23] an index of insulin resistance, would have  
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31 218 allowed us to assess the association between weight cycling and the physiological hazard of  
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33 219 diabetes. Third, the weight changes recorded in the rural region may be misclassified due to  
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35 220 missing data for the years when participants did not undergo the health examination.  
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37 221 However, such misclassification would bias the ORs to the null hypothesis, and we believe  
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39 222 such a bias would not change the conclusions for the rural region. Finally, a subset of the  
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41 223 diagnoses in this study was not made by physicians but by using an epidemiological  
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43 224 criterion.[12] However, most observational studies in nature rely on epidemiological criteria  
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45 225 for detecting diabetes, and the use of a consistent diagnostic criterion can allow researchers to  
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47 226 compare the risk of diabetes onset between groups of reference and interest.  
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54 227 The present study also has several strengths. First, to the best of our knowledge, this is the  
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56 228 first study to explore the relationship between weight cycling and the risk of diabetes in  
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3 229 Asians. Because the relationship was opposite to that in Americans, further research in East  
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5 230 Asians is necessary to confirm the relationship. Next, this study was conducted in two  
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7 231 differently characterised populations (urban and rural residents). The ORs of the risk of  
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9 232 diabetes were 1.05 (95%CI: 0.57–1.95) in the weight gain–loss pattern of the urban resident  
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11 233 women and 1.58 (95%CI: 0.78–3.17) in weight loss–gain pattern of the rural resident men.  
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14 234 However, all other weight cycling patterns in both sexes in urban and rural regions were  
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16 235 negatively correlated with the risk of diabetes. Third, the numbers of participants in both  
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18 236 sexes were approximately 10,000 in the urban region and approximately 5,000 in the rural  
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20 237 region. Because the present study included a large number of participants from both urban  
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22 238 and rural Japan, Japanese and East Asian weight cyclers can refer to its results.

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26 239 This study can contribute to helping public health practitioners and on-site clinical  
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28 240 professionals prevent diabetes in the general population. A sustained weight gain greater than  
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30 241 4% over ten years in middle age and more than 5 kg of additional weight gained since the age  
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32 242 of 20 years both carried increased risks of diabetes for both sexes. Because middle-aged  
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34 243 people can easily undergo such a small weight gain over the short or long term, non-diabetic  
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36 244 people within the normal BMI range should be cautious about the risks resulting from even  
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38 245 such a slight weight gain through their lifetime. An interventional study indicated that weight  
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40 246 loss ( $-1.8 \text{ kg/m}^2$  of BMI in a diet intervention group and  $-3.3 \text{ kg/m}^2$  of BMI in a  
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42 247 diet-and-exercise intervention group) improved insulin sensitivity in Japanese patients with  
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44 248 obesity and type 2 diabetes.[24] Improved insulin sensitivity was also observed in Americans  
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46 249 who maintained their weight with treadmill exercise and no alteration of diet.[25] In addition,  
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48 250 studies have demonstrated that building muscle through exercising without changing weight  
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50 251 improves insulin sensitivity.[26]



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3 252 In the present study, two profiles of weight cycling pattern resulted in an increase in the  
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5 253 risk of diabetes, whereas in the other six profiles the risk decreased. Because better insulin  
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7 254 sensitivity directly leads to a decreased risk of diabetes, the results may be due to the  
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10 255 differences in how the participants lost or gained weight (i.e. whether they lost or gained fat  
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12 256 or muscle mass). Recent studies have indicated that sarcopenia, the loss of skeletal muscle  
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14 257 alone or with increased fat mass in ageing, is a leading cause of death in old age.[27] The  
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16 258 present study results, in the context of previous studies, suggest that over both the short term  
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18 259 and long term, people can reduce their risk of diabetes by losing fat and maintaining muscle  
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## 25 26 27 262 **CONCLUSIONS**

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31 263 In urban and rural Japanese populations, weight cycling appears to reduce the risk of diabetes  
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33 264 in most patterns of weight change. The results may be attributable to the motivations of the  
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35 265 weight cyclers. The risk of diabetes increases linearly with weight gain from the age of 20  
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37 266 years in Japanese urban men and women. A study that includes the measurement of insulin  
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39 267 sensitivity is necessary to confirm the present results and to improve understanding of the  
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42 268 risks for East Asian weight cyclers.

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3 269 **Acknowledgments** We thank all participants in this study and staff at the St. Luke's  
4  
5 270 International Hospital and the Yamanashi Koseiren Health Care Center for their support,  
6  
7 271 which made this study possible.  
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10 272 **Competing interests** None declared.  
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13  
14 273 **Funding** This work was supported by the Ministry of Education, Culture, Sports, Science and  
15  
16 274 Technology of Japan (MEXT) (KAKENHI grant number: JP15K08730 and JP15K15221).  
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19  
20 275 **Contributors** ZY, YY, MT and OT: setting up the study and data collection. HY, ZY, MM  
21  
22 276 and AT: designing the study. HY and AT: data analysis. HY: writing and revising the draft. ZY,  
23  
24 277 SO, MM, YA and HY: development of the discussion section. All authors read and approved  
25  
26 278 the final manuscript.  
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28

29  
30 279 **Ethics approval** The ethics committee of the School of Medicine, University of Yamanashi  
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32 280 (approval number: H27-1417).  
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35 281 **Data sharing statement** No additional data are available.  
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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1	Line 1–2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Line 23–40
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Line 53–66
Objectives	3	State specific objectives, including any prespecified hypotheses	4	Line 66–67
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	4	Line 72–72
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4	Line 72–73
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5	Line 81–83
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5–6	Line 85–87, 93–102
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5–6	Line 93–102
Bias	9	Describe any efforts to address potential sources of bias	5	Line 83–90
Study size	10	Explain how the study size was arrived at	7	Line 126, 132

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6	Line 103–107
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6	Line 114–119
		(b) Describe any methods used to examine subgroups and interactions	6	Line 119
		(c) Explain how missing data were addressed	5	Line 83–85
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed		
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		NA
		(e) Describe any sensitivity analyses		NA
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7	Line 126, 132
		(b) Give reasons for non-participation at each stage	5	Line 83–85
		(c) Consider use of a flow diagram		NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7–8	Table 1
		(b) Indicate number of participants with missing data for each variable of interest		NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9–12	Table 2 and 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9–12	Table 2 and 3
		(b) Report category boundaries when continuous variables were categorized	9–12 (BMI)	Table 2 and 3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		NA

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Continued on next page Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		Table 2 and 3
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	12	Line 164–170
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14	Line 210–226
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12–14	Line 171–209
Generalisability	21	Discuss the generalisability (external validity) of the study results	15	Line 230–231
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17	Line 273–274

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).



# BMJ Open

## Weight cycling and the subsequent onset of type 2 diabetes mellitus in urban and rural Japan

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014684.R1
Article Type:	Research
Date Submitted by the Author:	17-Jan-2017
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<b>Primary Subject Heading</b>:	Diabetes and endocrinology
Secondary Subject Heading:	Health services research, Epidemiology, Nutrition and metabolism, Sports and exercise medicine
Keywords:	weight cycling, weight change, type 2 diabetes, body mass index, Asian

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Manuscripts

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3 1 **Weight cycling and the subsequent onset of type 2 diabetes mellitus in**  
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6 2 **urban and rural Japan**

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39 17 **Keywords:** weight cycling; weight change; type 2 diabetes; body mass index; Asian  
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44 19 **Word count: 3,243**  
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3 **ABSTRACT**

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6 **Objective:** To investigate how patterns in weight changes impact the risk of diabetes,  
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8 including those that occur after 20 years.  
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12 **Design:** Cohort study.

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15 **Setting:** Primary healthcare in urban and rural Japan.

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18 **Participants:** 20,708 urban and 9,670 rural residents.

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22 **Primary outcome measures:** Odds ratios (ORs) for diabetes in weight loss, loss-gain, stable,  
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24 gain-loss and weight gain for 10 years. Weight gain and loss were defined as a greater than  
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26  $\pm 4\%$  change from baseline weight.  
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31 **Results:** In the urban region, the ORs relative to the stable group for the loss-gain and  
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33 gain-loss groups were 0.63 (95% CI: 0.45–0.89) and 0.51 (95% CI: 0.32–0.82) for men and  
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35 0.72 (95% CI: 0.39–1.34) and 1.05 (95% CI: 0.57–1.95) for women, respectively. In the rural  
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37 region, they were 1.58 (95% CI: 0.78–3.17) and 0.44 (95% CI: 0.15–1.29) in men and 0.41  
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39 (95% CI: 0.12–1.44) and 0.77 (95% CI: 0.28–2.14) in women, respectively. The ORs for an  
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41 increase in weight between 5–10 kg from the age of 20 years were 1.54 (95% CI: 1.03–2.30)  
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43 in men and 0.96 (95% CI: 0.55–1.65) in women.  
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46 **Conclusions:** In Japan, weight cycling is associated with a significant reduction in the risk of  
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48 diabetes for men from an urban region and non-significantly for women from a rural region.  
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50 However, the associations are unclear for women from the urban region and in men of the  
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52 rural region. These results differ from those in Western studies, likely due to the motivations  
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54 underlying weight cycling.  
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44 **Word count: 251 words (limit: 300 words)**

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3 45 **Strengths and limitations of this study**

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6 46 ● In urban Japan, weight cyclers have a similar or lower risk of diabetes than people who  
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9 47 maintain a constant body weight.
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11 48 ● In urban and rural Japan, sustained weight gain increases the risk of diabetes.
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13 49 ● There is a dose–response relationship for both sexes between weight gain since the age  
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15 50 of 20 years and the risk of diabetes.
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17 51 ● Odds ratios may change according to the threshold of  $\pm 4\%$  weight change in 10 years.
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19 52 ● The levels of insulin secretion and sensitivity were not measured.
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3 **54 INTRODUCTION**

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6 **55** Weight gain is a well-known risk factor for incidental type 2 diabetes. Research involving  
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8 **56** people of Western, Oriental and African descent has quantitatively established the risks of  
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10 **57** developing diabetes in relation to weight gain.<sup>1-3</sup> Researchers have also raised the question of  
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12 **58** whether repeatedly gaining and losing weight (weight cycling) is an independent risk factor  
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14 **59** for developing diabetes due to gaining weight. Studies on this topic are inconsistent in  
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16 **60** Westerners of Europe and the United States, and researchers currently appear to recognise  
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18 **61** that weight cycling may not independently increase but strongly induce the risk of diabetes.  
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20 **62** <sup>4-8</sup> In contrast, the risk of diabetes in Asian weight cyclers has not been researched.

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25 **63** Due to the preconception linking being slim to an aesthetic standard,<sup>9 10</sup> many Asian  
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27 **64** women make an effort to lose weight.<sup>11 12</sup> Another group likely to try to reduce weight are  
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29 **65** middle-aged East Asian businesspeople who have gained weight but have few opportunities  
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31 **66** for physical activity. Recent studies have demonstrated that East Asians are much more likely  
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33 **67** than Westerners to develop type 2 diabetes at a lower body mass index (BMI).<sup>13</sup> As a result, it  
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35 **68** may take only a small change in weight to alter the risk of diabetes for East Asians. In  
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37 **69** addition, the literature indicates that in Japan, diet, physical activity, prevalence of  
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39 **70** overweight individuals and aesthetic consciousness of metropolitan residents are different  
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41 **71** from those of rural residents.<sup>14 15</sup> The aim of this study was to establish whether weight  
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43 **72** cyclers residing in Japan were at an increased risk of diabetes. We used Japanese urban and  
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45 **73** rural data to examine this clinical question in populations with varying lifestyles.

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53 **75 METHODS**

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55 **76 Study participants and measurements**

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77 In this cohort study, we enrolled participants from an urban area, Tokyo Metropolis and a  
78 rural area, Yamanashi Prefecture. In Tokyo, we enrolled employees of private companies who  
79 underwent medical check-ups between January 2005 and December 2014 at St. Luke's  
80 International Hospital. These annual medical check-ups were based on a legal obligation  
81 imposed by the Industrial Safety and Health Act in Japan.<sup>16</sup> In the Yamanashi Prefecture, we  
82 enrolled employees and residents who paid for a private comprehensive medical check-up  
83 service between April 1999 and March 2009 at the Yamanashi Koseiren Health Care Center.  
84 A subset of participants in Yamanashi used a subsidy from their employers or administrative  
85 agencies to receive the private medical check-up. Thus, the participants in the urban area  
86 received almost annual medical check-ups over 10 years, and those in the rural area received  
87 occasional voluntary check-ups. Participants were included in the analysis if they had no  
88 diagnosis of diabetes and an HbA1c less than 6.5% (48 mmol/mol) during a baseline period  
89 for the first three years of the 10-year period. If they received medical check-ups two or three  
90 times during the first three years, the data from the first visit were adopted for the baseline.  
91 Those included were also required to undergo a medical check-up at least twice during the  
92 latter seven years of the study. Hence, participants needed to receive at least three medical  
93 check-ups for the categorisation of weight change patterns (exposure). The onset of diabetes  
94 was identified through questionnaires for the diagnosis of diabetes, the commencement of  
95 diabetic therapies or glycated haemoglobin (HbA1c)  $\geq$  6.5% (48 mmol/mol).<sup>17 18</sup> At the  
96 institution in Tokyo, trained nurses interviewed the participants from the age of 20 years to  
97 establish their changes in weight. BMI was calculated as the participant's weight in kilograms  
98 divided by the square of their height in metres.

100 **Weight change categories**

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3 101 The participants were categorised into five groups according to their patterns of weight  
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5 102 change during the 3–10 years since the baseline period. The stable group was comprised of  
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7 103 the participants whose weight had not changed from the baseline by more than  $\pm 4\%$ . The  
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9 104 sustained gain group consisted of the participants who gained more than 4% of their baseline  
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11 105 weight and did not subsequently lose this extra weight. Similarly, the sustained loss group  
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13 106 was comprised of participants who lost more than 4% of their baseline weight and did not  
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15 107 subsequently regain this weight. The gain-loss group included participants who gained more  
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17 108 than 4% of their baseline weight but brought their weight back below +4%. The loss-gain  
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19 109 group included participants who lost more than 4% of their baseline weight but brought their  
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21 110 weight back above  $-4\%$ . From the last time point of this categorisation, the outcome of  
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23 111 incident diabetes was measured. Therefore, the duration of observing whether the participants  
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25 112 developed diabetes was between one and six years among the categories. The incidence of  
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27 113 diabetes was measured after the participants were categorised, and any data measured after a  
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29 114 diagnosis of diabetes were ignored to conserve the temporality of exposure to outcome for an  
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31 115 epidemiological causation.<sup>19</sup> The incidence of diabetes was measured after the participants  
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33 116 were categorised, and any data measured after a diagnosis of diabetes were ignored to  
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35 117 conserve the temporality of exposure to outcome for an epidemiological causation.  
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42 118 The  $\pm 4\%$  change in weight used for this categorisation was determined as approximately a  
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44 119 one-unit change for a person with a BMI of  $22 \text{ kg/m}^2$ . This was based on the 2014 reference  
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46 120 mean BMIs for Japanese men and women of  $23.6 \text{ kg/m}^2$  and  $21.7 \text{ kg/m}^2$ , respectively.<sup>20</sup> It  
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48 121 also took into consideration the relatively short time period of ten years for the observation.  
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50 122 The gain-loss and loss-gain group of participants were the weight cyclers of interest.  
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## 55 124 **Statistical analysis**

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3 125 The baseline characteristics recorded for the participants included age, weight, height, BMI,  
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5 126 HbA1c and fasting plasma glucose. We used univariate and multivariate logistic regressions  
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7 127 to compare the risk of diabetes between the categorised groups. In the urban data of Tokyo  
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9 128 Metropolis, the covariates used for the adjustment at baseline were age, weight change from  
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11 129 20 years of age, BMI, smoking habits, alcohol consumption and physical activity. In the rural  
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13 130 data of the Yamanashi Prefecture, the available covariates for the adjustment at baseline were  
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15 131 age, BMI, smoking habit and alcohol consumption. The analyses were stratified by sex. In  
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17 132 addition, another focus of this study was the impact of weight cycling on incidental diabetes  
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19 133 in middle-aged individuals. Hence, for a sensitivity analysis, we restricted the analyses to a  
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21 134 middle-aged population of 45 to 64 years. All statistical analyses were performed using SAS  
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23 135 statistical software (version 9.3, SAS Institute, NC, USA). The descriptive statistics are  
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25 136 reported as the means and standard deviations (SD). All reported p values were two-sided; *P*  
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27 137 values of <0.05 were considered to be statistically significant.  
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## 35 139 **RESULTS**

### 37 140 **Participants**

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41 141 For the multivariate analyses of primary interest, 10,094 men and 10,614 women were  
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43 142 enrolled from Tokyo Metropolis (Table 1). The means (SDs) of the baseline characteristics  
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45 143 for the men in the urban region were as follows: age 49.6 (11.9) years, weight 68.8 (9.7) kg,  
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47 144 BMI 23.7 (2.8) kg/m<sup>2</sup> and HbA1c 5.4% (0.3%) (35.3 [3.7] mmol/mol). For the women in the  
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49 145 urban region, these values were as follows: age 48.3 (11.3) years, weight 52.3 (7.4) kg, BMI  
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51 146 21.0 (2.9) kg/m<sup>2</sup> and HbA1c 5.3% (0.4%) (35.0 [3.8] mmol/mol).  
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55 147 Table 1 also shows the baseline characteristics of 4,818 men and 4,852 women enrolled  
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57 148 from the Yamanashi Prefecture. The baseline characteristics for the men in the rural region  
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149 were as follows: age 51.2 (10.3) years, weight 65.7 (9.1) kg, BMI 23.2 (2.7) kg/m<sup>2</sup> and  
 150 HbA1c 5.3% (0.3%) (34.3 [3.8] mmol/L). For the women in the rural area, the values were as  
 151 follows: age 52.1 (9.4) years, weight 53.1 (7.5) kg, BMI 22.1 (2.9) kg/m<sup>2</sup> and HbA1c 5.3%  
 152 (0.3%) (34.4 [3.5] mmol/L).

153 **Table 1. Baseline characteristics of the participants from urban (Tokyo Metropolis) and**  
 154 **rural (Yamanashi Prefecture) regions of Japan.**

Characteristics, mean (standard deviation)	Men	Women
<b>Urban region</b>		
No.	10,094	10,614
Age, years	49.6 (11.9)	48.3 (11.3)
Weight, kg	68.8 (9.7)	52.3 (7.4)
Height, cm	170.4 (6.1)	157.7 (5.6)
Body mass index, kg/m <sup>2</sup>	23.7 (2.8)	21.0 (2.9)
HbA1c, %	5.4 (0.3)	5.3 (0.4)
(HbA1c, mmol/mol)	35.3 (3.7)	35.0 (3.8)
Fasting plasma glucose, mg/dL	100.8 (8.6)	94.5 (8.0)
(Fasting plasma glucose, mmol/L)	5.6 (0.5)	5.2 (0.4)
<b>Rural region</b>		
No.	4,818	4,852
Age, years	51.2 (10.3)	52.1 (9.4)
Weight, kg	65.7 (9.1)	53.1 (7.5)
Height, cm	168.1 (6.2)	154.8 (5.6)
Body mass index, kg/m <sup>2</sup>	23.2 (2.7)	22.1 (2.9)
HbA1c, %	5.3 (0.3)	5.3 (0.3)
(HbA1c, mmol/mol)	34.3 (3.8)	34.4 (3.5)
Fasting plasma glucose, mg/dL	96.3 (9.0)	93.2 (8.5)
(Fasting plasma glucose, mmol/L)	5.3 (0.5)	5.2 (0.5)

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156 **Risk of diabetes in urban and rural Japan**

157 Tables 2 and 3 present the incidence of diabetes and the odds ratios (ORs) for each  
 158 explanatory variable in the urban and rural regions, respectively. For the men in the urban  
 159 region, the adjusted ORs (95% confidence intervals [95% CIs]) compared to the stable group  
 160 were 3.07 (2.15–4.39) in the sustained gain group, 0.51 (0.32–0.82) in the gain-loss group,  
 161 0.63 (0.45–0.89) in the loss-gain group and 1.11 (0.77–1.59) in the sustained loss group. For  
 162 the women in the urban region, the adjusted ORs relative to the stable group were 7.00 (4.11–  
 163 11.94) in the sustained gain group, 1.05 (0.57–1.95) in the gain-loss group, 0.72 (0.39–1.34)  
 164 in the loss-gain group and 1.48 (0.80–2.74) in the sustained loss group. For the men in the  
 165 rural region, the adjusted ORs were 3.15 (1.70–5.83) in the sustained gain group, 0.44 (0.15–  
 166 1.29) in the gain-loss group, 1.58 (0.78–3.17) in the loss-gain group and 0.36 (0.12–1.05) in  
 167 the sustained loss group. For the women in the rural region, the adjusted ORs were 1.43  
 168 (0.59–3.48) in the sustained gain group, 0.77 (0.28–2.14) in the gain-loss group, 0.41 (0.12–  
 169 1.44) in the loss-gain group and 0.32 (0.09–1.10) in the sustained loss group.

170 **Table 2. The incidence and odds ratios (95% CIs) of diabetes related to patterns of**  
 171 **weight change over 10 years in residents of urban Japan**

Exposure variables		Acquired DM / No. of subjects (incidence, %)	Crude	Multivariate
<b>Men (No. For multivariate analysis =10,094)</b>				
Baseline age	Per 10 years	—	1.44 (1.33–1.55)	1.44 (1.29–1.61)
	< -5	7/1438 (0.5)	2.18 (1.14–4.18)	1.68 (0.75–3.80)
Weight change from 20 years of age, kg	-5 to +5	73/10646 (0.7)	Ref	Ref
	+5 to +10	31/3200 (1.0)	1.98 (1.45–2.72)	1.54 (1.03–2.30)
	> +10	78/2166 (3.6)	3.37 (2.54–4.48)	2.08 (1.40–3.10)
Baseline BMI,	< 18.5	6/387 (1.6)	1.35 (0.57–3.16)	0.88 (0.29–2.70)

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	kg/m <sup>2</sup>	18.5–22	49/4236 (1.2)	Ref	Ref
		22–25	168/7220 (2.3)	2.04 (1.48–2.89)	1.73 (1.14–2.63)
		> 25	190/4699 (4.0)	3.60 (2.62–4.94)	2.52 (1.60–3.95)
Weight change pattern over 10 years	Sustained loss		66/1903 (3.5)	1.39 (1.03–1.87)	1.11 (0.77–1.59)
	Loss–gain		87/4644 (1.9)	0.74 (0.56–0.97)	0.63 (0.45–0.89)
	Stable		142/5621 (2.5)	Ref	Ref
	Gain–loss		38/3063 (1.2)	0.49 (0.34–0.70)	0.51 (0.32–0.82)
	Sustained gain		80/1311 (6.1)	2.51 (1.89–3.32)	3.07 (2.15–4.39)
Smoking	None		123/6385 (1.9)	Ref	Ref
	Ex-smoker		150/5940 (2.5)	1.32 (1.04–1.68)	0.97 (0.71–1.31)
	Current smoker		140/4217 (3.3)	1.75 (1.37–2.23)	1.73 (1.25–2.34)
Alcohol drinking	None		69/2250 (3.1)	Ref	Ref
	Sometimes		48/1667 (2.9)	0.94 (0.65–1.36)	0.96 (0.66–1.40)
	Usually		156/6177 (2.5)	0.82 (0.61–1.09)	0.78 (0.58–1.05)
Duration of walking per day	Per 30 min	—	0.996 (0.92–1.08)	1.01 (0.92–1.11)	
Physical activity	0–1/week		85/3282 (2.6)	Ref	Ref
	1–2/week		108/4105 (2.6)	1.02 (0.76–1.36)	1.02 (0.76–1.36)
	3–5/week		43/1541 (2.8)	1.08 (0.74–1.57)	0.98 (0.67–1.45)
	6–7/week		37/1166 (3.2)	1.23 (0.83–1.82)	1.06 (0.69–1.62)
<b>Women (No. for multivariate analysis = 10,614)</b>					
Baseline age	Per 10 years	—	1.66 (1.48–1.87)	1.78 (1.50–2.12)	
Weight change from 20 years of age, kg	< –5		11/439 (2.5)	0.71 (0.33–1.54)	0.48 (0.18–1.25)
	–5 to +5		61/5243 (1.2)	Ref	Ref
	+5 to +10		109/4779 (2.3)	1.42 (0.93–2.16)	0.96 (0.55–1.65)
	> +10		232/6081 (3.8)	5.41 (3.92–7.47)	2.10 (1.20–3.67)
Baseline BMI, kg/m <sup>2</sup>	< 18.5		20/2916 (0.7)	1.24 (0.74–2.08)	1.47 (0.76–2.86)
	18.5–22		52/9388 (0.6)	Ref	Ref
	22–25		60/3676 (1.6)	2.98 (2.05–4.33)	2.01 (1.21–3.34)
	> 25		57/1470 (3.9)	7.24 (4.95–10.59)	2.91 (1.53–5.52)
Weight change pattern over 10 years	Sustained loss		24/1661 (1.4)	2.11 (1.25–3.54)	1.48 (0.80–2.74)
	Loss–gain		32/4022 (0.7)	1.15 (0.72–1.86)	0.72 (0.39–1.34)
	Stable		36/5212 (1.3)	Ref	Ref

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	Gain–loss	30/4630 (0.6)	0.94 (0.58–1.53)	1.05 (0.57–1.95)
	Sustained gain	67/1925 (3.5)	5.19 (3.45–7.80)	7.00 (4.11–11.94)
	None	156/14,194 (1.1)	Ref	Ref
Smoking	Ex-smoker	17/1789 (1.0)	0.86 (0.52–1.143)	0.85 (0.45–1.61)
	Current smoker	16/1467 (1.1)	0.99 (0.59–1.67)	1.20 (0.63–2.32)
	None	78/5669 (1.4)	Ref	Ref
Alcohol drinking	Sometimes	20/2035 (1.0)	0.71 (0.43–1.17)	0.91 (0.55–1.52)
	Usually	27/2910 (0.9)	0.67 (0.43–1.04)	0.95 (0.60–1.51)
Duration of walking per day	Per 30 min	—	1.01 (0.93–1.11)	1.01 (0.90–1.13)
	0–1/week	37/3894 (1.0)	Ref	Ref
Physical activity	1–2/week	42/3760 (1.1)	1.18 (0.76–1.84)	1.11 (0.70–1.75)
	3–5/week	27/1874 (1.4)	1.52 (0.93–2.52)	1.14 (0.67–1.94)
	6–7/week	19/1086 (1.7)	1.86 (1.06–3.24)	1.43 (0.79–2.60)

172 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

173 **Table 3. The incidence and odds ratios (95% CIs) of diabetes related to patterns of**  
 174 **weight change over 10 years in residents of rural Japan**

Exposure variables		Acquired DM / No. of subjects (incidence, %)	Crude	Multivariate
<b>Men (No. for multivariate analysis = 4818)</b>				
Baseline age	Per 10 years	—	1.36 (1.08–1.72)	1.60 (1.24–2.05)
	< 18.5	0/167 (0)	—	—
Baseline BMI, kg/m <sup>2</sup>	18.5–22	10/1425 (0.7)	Ref	Ref
	22–25	21/2079 (1.0)	1.44 (0.68–3.08)	1.69 (0.79–3.63)
	> 25	35/1148 (3.1)	4.45 (2.19–9.03)	5.81 (2.82–11.97)
Weight change pattern over 10 years	Sustained loss	4/725 (0.6)	0.43 (0.15–1.25)	0.36 (0.12–1.05)
	Loss–gain	13/681 (1.9)	1.50 (0.75–3.00)	1.58 (0.78–3.17)
	Stable	22/1719 (1.3)	Ref	Ref
	Gain–loss	4/916 (0.4)	0.34 (0.12–0.99)	0.44 (0.15–1.29)
	Sustained gain	23/778 (3.0)	2.35 (1.30–4.24)	3.15 (1.70–5.83)

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	None	23/1695 (1.4)	Ref	Ref
Smoking	Ex-smoker	8/998 (0.8)	0.59 (0.26–1.32)	0.72 (0.32–1.64)
	Current smoker	35/2126 (1.7)	1.22 (0.72–2.07)	1.50 (0.85–2.62)
Drinking	None	11/1071 (1.0)	Ref	Ref
	Drinker	55/3748 (1.5)	1.44 (0.75–2.75)	1.52 (0.79–2.94)
<b>Women (No. for multivariate analysis = 4852)</b>				
Baseline age	Per 10 years	—	1.43 (0.99–2.06)	1.23 (0.83–1.84)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	0/411 (0)	—	—
	18.5–22	7/2135 (0.3)	Ref	Ref
	22–25	14/1563 (0.9)	2.75 (1.11–6.82)	2.69 (1.07–6.75)
	> 25	13/744 (1.8)	5.41 (2.15–13.60)	5.29 (2.07–13.51)
Weight change pattern over 10 years	Sustained loss	3/863 (0.3)	0.37 (0.11–1.29)	0.32 (0.09–1.10)
	Loss–gain	3/757 (0.4)	0.42 (0.12–1.47)	0.41 (0.12–1.44)
	Stable	15/1615 (0.9)	Ref	Ref
	Gain–loss	5/827 (0.6)	0.65 (0.24–1.79)	0.77 (0.28–2.14)
	Sustained gain	8/791 (1.0)	1.09 (0.46–2.58)	1.43 (0.59–3.48)
Smoking	None	2/646 (0.3)	Ref	Ref
	Ex-smoker	29/3822 (0.8)	2.45 (0.58–10.31)	2.19 (0.52–9.26)
	Current smoker	3/375 (0.8)	2.60 (0.43–15.60)	3.33 (0.55–20.28)
Drinking	None	31/3542 (0.9)	Ref	Ref
	Drinker	3/1311 (0.2)	0.26 (0.08–0.85)	0.29 (0.09–0.95)

175 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

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177 Table 4 shows the risk of diabetes risk due to weight cycling in the middle-aged population.

178 The ORs (95% CIs) for incidental diabetes were 0.57 (0.32–1.01) in the gain-loss group and

179 0.74 (0.49–1.11) in the loss-gain group among men living in the urban area. The

180 corresponding ORs (95% CIs) were 0.80 (0.36–1.77) and 0.76 (0.37–1.57), respectively

181 among women living in the urban area; 0.58 (0.19–1.77) and 1.76 (0.80–3.87), respectively

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182 among men living in rural area. The ORs were 0.82 (0.26–2.62) and 0.54 (0.15–1.94),  
183 respectively among the women living in the rural area.

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185 **Table 4. The incidence and odds ratios of diabetes related to patterns of weight change over 10 years**  
186 **in middle-aged residents (45–64 years) in Japan**

Exposure variables	Acquired DM / No. of subjects (incidence, %)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	
<b>Urban middle-aged men (No. for multivariate analysis =4,882)</b>				
Weight change pattern over 10 years	Sustained loss	35/981 (3.6)	1.04 (0.65–1.67)	0.97 (0.60–1.55)
	Loss-gain	62/2203 (2.8)	0.79 (0.53–1.18)	0.74 (0.49–1.11)
	Stable	100/2749 (3.6)	Ref	Ref
	Gain-loss	26/1098 (2.4)	0.56 (0.32–0.999)	0.57 (0.32–1.01)
	Sustained gain	50/489 (10.2)	3.09 (2.00–4.76)	3.13 (2.00–4.89)
<b>Urban middle-aged women (No. for multivariate analysis = 5,053)</b>				
Weight change pattern over 10 years	Sustained loss	15/994 (1.5)	1.30 (0.62–2.73)	1.13 (0.53–2.41)
	Loss-gain	20/1992 (1.0)	0.87 (0.43–1.77)	0.76 (0.37–1.57)
	Stable	24/2285 (1.1)	Ref	Ref
	Gain-loss	17/1642 (1.0)	0.74 (0.34–1.62)	0.80 (0.36–1.77)
	Sustained gain	40/603 (6.6)	5.62 (3.05–10.37)	6.97 (3.67–13.25)
<b>Rural middle-aged men (No. for multivariate analysis =2,937)</b>				
Weight change pattern over 10 years	Sustained loss	3/447 (0.7)	0.48 (0.14–1.66)	0.42 (0.12–1.47)
	Loss-gain	11/449 (2.5)	1.78 (0.81–3.91)	1.76 (0.80–3.87)
	Stable	15/1078 (1.4)	Ref	Ref
	Gain-loss	4/546 (0.7)	0.52 (0.17–1.58)	0.58 (0.19–1.77)
	Sustained gain	12/417 (2.9)	2.10 (0.98–4.53)	2.48 (1.12–5.49)
<b>Rural middle-aged women (No. for multivariate analysis = 3,347)</b>				
Weight change pattern over 10 years	Sustained loss	1/638 (0.2)	0.16 (0.02–1.25)	0.14 (0.02–1.01)
	Loss-gain	3/579 (0.5)	0.54 (0.15–1.92)	0.54 (0.15–1.94)
	Stable	11/1140 (1.0)	Ref	Ref
	Gain-loss	4/558 (0.7)	0.74 (0.24–2.34)	0.82 (0.26–2.62)
	Sustained gain	5/432 (1.2)	1.20 (0.42–3.48)	1.30 (0.44–3.84)

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3 187 Multivariate logistic regression calculated odds ratios with an adjustment for baseline age and BMI, weight  
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5 188 change from 20 years of age, smoking and drinking habits, duration of walking per day and physical activity  
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7 189 per week in the urban data. The baseline age and BMI and smoking and drinking habits in the rural data.  
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5 191 **DISCUSSION**  
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8 192 The data for the urban region suggest that the risk of diabetes in male and female weight  
9 193 cyclers was similar to or lower than that of the participants who maintained a stable  
10 194 weight. In particular, the data for Japanese men residing in an urban region indicate that,  
11 195 compared with the men who maintained a stable weight, there was a significantly  
12 196 reduced risk of diabetes associated with weight cycling. The data for Japanese women  
13 197 residing in a rural region also suggest a reduced risk of diabetes with weight cycling  
14 198 compared with maintaining a stable weight. These results are reinforced by a sensitivity  
15 199 analysis with a restriction on middle-aged individuals, representing almost same ORs as  
16 200 those in the entire population except for the OR in the gain-loss group among women  
17 201 residing in the urban region.  
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32 202 These observations are not consistent with those from previous studies of Western  
33 203 populations, which showed that weight cycling significantly or non-significantly  
34 204 increased the risk of diabetes for point estimates. In the Framingham Heart Study,  
35 205 approximately 1 kg/m<sup>2</sup> of weight cycling in middle-aged Americans carried a hazard  
36 206 ratio of 1.1 (95%CI: 0.8–1.5) for the risk of diabetes after adjusting for sex and BMI at  
37 207 25 years of age.<sup>4</sup> In the American middle-aged women of the National Health and  
38 208 Nutrition Examination Survey, weight cycling of 4.5–9.1 kg and 9.1–22.2 kg with an  
39 209 intentional weight loss three or more times in four years carried ORs for the risk of  
40 210 diabetes of 1.11 (95%CI: 0.89–1.37) and 1.39 (95%CI: 0.90–2.13), respectively.<sup>5</sup> A  
41 211 study from a cohort of medical students at the Johns Hopkins University School of  
42 212 Medicine reported that the highest quartile of BMI variability for ages between 25 and  
43 213 45 years had an OR of 2.1 (95%CI: 1.0–4.6) for the risk of diabetes after 50 years,  
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5 214 compared with the other three lower quartiles.<sup>21</sup> In a large German cohort, weight  
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7 215 cycling of  $\geq 1.5$  kg/year was significantly associated with an adjusted hazard ratio of  
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9 216 1.34.<sup>6</sup>

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13 217 The inconsistency between the Western studies and this study that weight cycling was  
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15 218 not associated with an increase in the risk of diabetes but may even reduce the risk, may  
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17 219 be due to ethnic differences in diet,<sup>22</sup> the capacity to gain weight<sup>23</sup> and  
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19 220 self-consciousness about body weight.<sup>24</sup> Further research is required to explore why the  
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21 221 relationship between weight cycling and risk of diabetes is inversed between Western  
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23 222 and East Asian populations. The reason may be attributable to different motivations to  
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25 223 lose weight in the context of different diet cultures and body self-consciousness.<sup>25</sup> The  
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27 224 East Asians who try to lose weight may be particularly those who are relatively  
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29 225 concerned about the poor health outcomes of being overweight. Westerners described in  
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31 226 the study cohorts who tried to lose weight may, in an extreme expression, have been  
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33 227 those who lost and regained a great deal of weight and potentially ran the risk of poor  
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35 228 health outcomes.

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40 229 From the data from the urban region, a weight increase of more than +5 kg above the  
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42 230 participant's weight at the age of 20 years increased the risk of developing diabetes with  
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44 231 a dose-response relationship in both men and women (Table 2). Furthermore, in both  
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46 232 sexes, an increase in weight of more than +10 kg above that when aged 20 years more  
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48 233 than doubles the risk of diabetes, with statistical significance, compared to the risk for  
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50 234 those who maintained their weight within  $\pm 5$  kg of their weight when aged 20 years.  
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52 235 These results agree with the study involving a US cohort, which reported a relative risk  
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54 236 of 3.2 (95%CI: 1.4–7.4) for the highest quartile of an increase in BMI from 25 to 45  
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5 237 years of age in comparison with the other three lower quartiles.<sup>21</sup> A dose–response  
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7 238 relationship of weight change from that aged 20 years to the risk of diabetes occurred in  
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9 239 the Japanese women residing in the urban region, with ORs of 0.48 (95%CI: 0.18–1.25)  
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11 240 for a change less than 5 kg, 0.96 (95%CI: 0.55–1.65) for an increase of between 5 and  
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13 241 10 kg and 2.10 (95%CI: 1.20–3.67) for an increase greater than 10 kg. In contrast, the  
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15 242 Japanese men who had lost 5 kg or more of body weight between the age of 20 years  
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17 243 and early middle age had an OR of 1.68 (95%CI: 0.75–3.80). This paradoxically  
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19 244 increased OR was most likely due to the small number of participants (seven) who  
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21 245 developed diabetes among a weight loss group of 1438 people.  
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26 246 This study had several limitations. The first of these was the threshold of  $\pm 4\%$  weight  
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28 247 change in 10 years. This threshold referred to a study from United Kingdom on the  
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30 248 association between weight change and the risk of diabetes.<sup>26</sup> The threshold of a  $\pm 4\%$   
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32 249 weight change was calculated as approximately 1 BMI unit in Japanese people with a  
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34 250 mean BMI of 23 kg/m<sup>2</sup>. However, the threshold for categorisation of weight cycling  
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36 251 should vary according to mean BMIs in different ethnicities, in which people have  
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38 252 different insulin sensitivities.<sup>13 27</sup> Second, we did not evaluate insulin sensitivity.  
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40 253 Measuring fasting plasma glucose and insulin concentration to calculate HOMA-IR,<sup>28</sup>  
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42 254 an index of insulin resistance, would have allowed us to assess the association between  
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44 255 weight cycling and the physiological hazard of diabetes. Third, the weight changes  
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46 256 recorded in the rural region may be misclassified due to missing data for the years when  
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48 257 participants did not undergo the health examination. However, such misclassification  
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50 258 would bias the ORs to the null hypothesis, and we believe that such a bias would not  
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52 259 change the conclusions for the rural region. Fourth, we could not examine whether the  
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5 260 weight cycling was intentional; however, we consider that a subset of unintentional  
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7 261 weight loss could be attributed to metabolic diseases, and patients with such diseases  
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9 262 could not usually regain the weight within a short duration. Fifth, the urban data for the  
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11 263 weight at 20 years of age were derived from the participants' memory. Thus, recall bias  
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13 264 could have existed in the results. Sixth, a subset of the diagnoses in this study were not  
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15 265 made by physicians but via an epidemiological criteria.<sup>17</sup> However, most observational  
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17 266 studies by nature rely on epidemiological criteria for detecting diabetes, and the use of a  
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19 267 consistent diagnostic criterion can allow researchers to compare the risk of diabetes  
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21 268 onset between the reference group and that of interest. Last, this study lacks the  
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23 269 information pertaining to lifestyle, including diet, marriage status, job type and owning  
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25 270 a car, that may have partly explain the association between weight cycling and incident  
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27 271 diabetes.  
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33 272 The present study also has several strengths. First, to the best of our knowledge, this  
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35 273 is the first study to explore the relationship between weight cycling and the risk of  
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37 274 diabetes in Asians. Since the relationship in this study was opposite to that of Americans,  
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39 275 further research in East Asians is necessary to confirm this relationship. Next, this study  
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41 276 was conducted in two differently characterised populations (urban and rural residents).  
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43 277 The ORs of the risk of diabetes were 1.05 (95%CI: 0.57–1.95) in the weight gain-loss  
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45 278 pattern of the urban resident women and 1.58 (95%CI: 0.78–3.17) in weight loss-gain  
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47 279 pattern of the rural resident men. However, all other weight cycling patterns for both  
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49 280 sexes in the urban and rural regions were negatively correlated with the risk of diabetes.  
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51 281 Third, the number of participants in both sexes were approximately 10,000 in the urban  
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53 282 region and approximately 5,000 in the rural region. Since the present study included a  
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283 large number of participants from both urban and rural Japan, Japanese and East Asian  
284 weight cyclers can refer to its results.

285 This study can contribute to aiding public health practitioners and on-site clinical  
286 professionals prevent diabetes in the general population. A sustained weight gain greater  
287 than 4% over ten years in middle age and more than 5 kg of additional weight gained  
288 since the age of 20 years both carried an increased risk of diabetes for both sexes. Since  
289 middle-aged people can easily undergo such a small weight gain over the short or long  
290 term, non-diabetic people within the normal BMI range should be cautious about the  
291 risks resulting from even such a slight weight gain through their lifetime. An  
292 interventional study indicated that weight loss ( $-1.8 \text{ kg/m}^2$  of BMI in a diet intervention  
293 group and  $-3.3 \text{ kg/m}^2$  of BMI in a diet-and-exercise intervention group) improved  
294 insulin sensitivity in Japanese patients with obesity and type 2 diabetes.<sup>29</sup> Improved  
295 insulin sensitivity was also observed in Americans who maintained their weight with  
296 treadmill-based exercise and no alteration in their diet.<sup>30</sup> In addition, studies have  
297 demonstrated that building muscle through exercising without changing weight  
298 improves insulin sensitivity.<sup>31</sup>

299 In the present study, two profiles of weight cycling pattern resulted in an increase in  
300 the risk of diabetes, whereas the risk decreased in the other six profiles. Since better  
301 insulin sensitivity directly leads to a decreased risk of diabetes, the results may be due  
302 to the differences in how the participants lost or gained weight (i.e. whether they lost or  
303 gained fat or muscle mass). Recent studies have indicated that sarcopenia, the loss of  
304 skeletal muscle alone or with increased fat mass in ageing, is a leading cause of death in  
305 old age.<sup>32</sup> The results of the present study, in the context of previous studies, suggest

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5 306 that over both the short- and long-term, people can reduce their risk of diabetes by  
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7 307 losing fat and maintaining muscle mass.  
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14 309 **CONCLUSIONS**

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17 310 In men in the urban region and women of rural region in Japan, weight cycling has been  
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19 311 associated with a reduction in the risk of diabetes, with statistical significance and  
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21 312 non-significance, respectively; however, a clear association was not observed in the  
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23 313 women of the urban region and men of the rural region. The results were different than  
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25 314 those in Western countries and may be attributed to the motivations of the weight  
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27 315 cyclers. In addition, the risk of diabetes increases linearly with weight gain from the age  
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29 316 of 20 years in Japanese urban men and women. A study that includes the measurement  
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31 317 of insulin sensitivity is necessary to confirm the present results and to improve the  
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33 318 understanding of the risks for East Asian weight cyclers.  
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38 319 **(3,243 words; limit of 4,000 words)**  
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5 320 **Acknowledgments** We thank all participants in this study and staff at the St. Luke's  
6  
7 321 International Hospital and the Yamanashi Koseiren Health Care Center for their support,  
8  
9 322 which made this study possible.  
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13 323 **Competing interests** None declared.  
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15  
16 324 **Funding** This work was supported by the Ministry of Education, Culture, Sports,  
17  
18 325 Science and Technology of Japan (MEXT) (KAKENHI grant number: JP15K08730 and  
19  
20 326 JP15K15221).  
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24 327 **Contributors** ZY, YY, MT and OT: setting up the study and data collection. HY, ZY,  
25  
26 328 MM and AT: designing the study. HY and AT: data analysis. HY: writing and revising  
27  
28 329 the draft. ZY, SO, MM, YA and HY: development of the discussion section. All authors  
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30 330 read and approved the final manuscript.  
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34 331 **Ethics approval** The ethics committee of the School of Medicine, University of  
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36 332 Yamanashi (approval number: H27-1417).  
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39 333 **Data sharing statement** No additional data are available.  
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5 424 **Figure 1. Scheme of how participants were categorised into the five**  
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8 425 **weight change patterns**  
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## Categorisation of weight change patterns

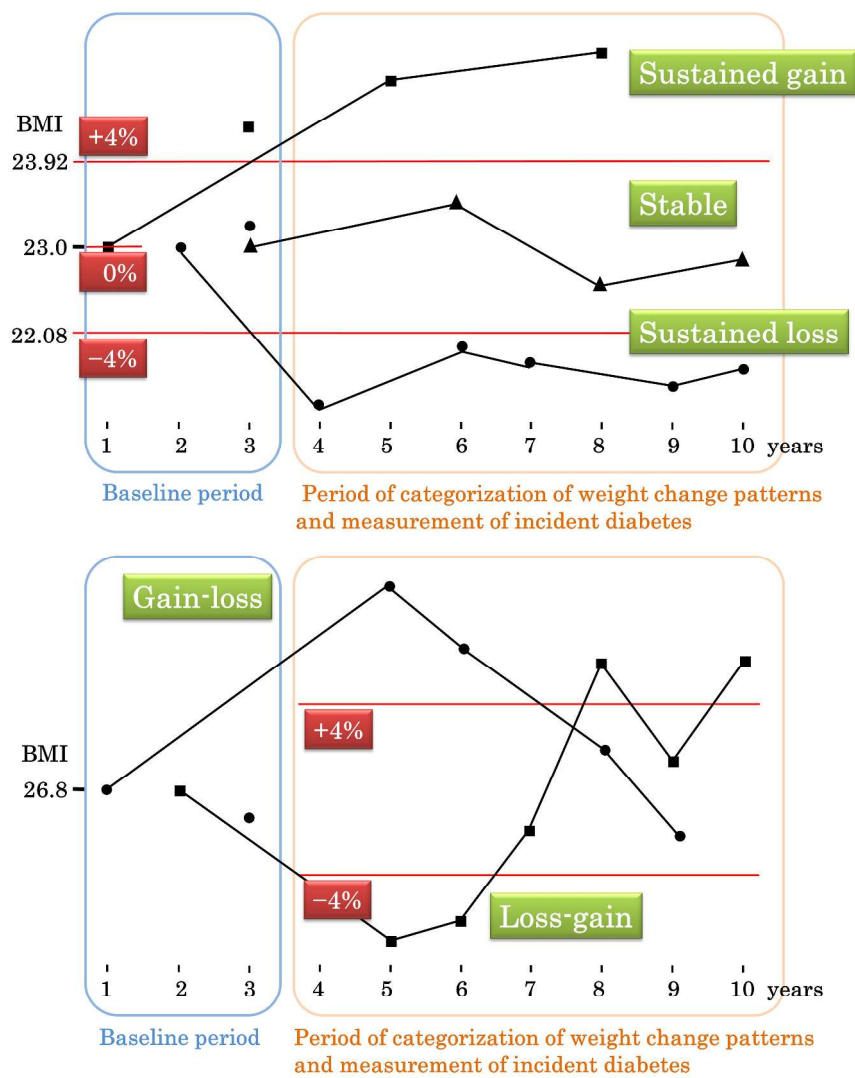


Figure 1  
Scheme of how participants were  
339x454mm (300 x 300 DPI)

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**Supplementary. Baseline characteristics among groups of weight change patterns over 10 years**

<b>Men in urban Japan (n = 10,094)</b>	Sustained loss	Loss-gain	Stable	Gain-loss	Sustained gain
Age, years	52.3 (12.2)	51.2 (12.0)	50.3 (11.3)	46.0 (11.4)	44.9 (11.3)
Weight, kg	70.8 (10.4)	69.8 (9.5)	68.3 (9.0)	67.3 (9.5)	67.8 (10.8)
Height, cm	170.1 (6.2)	170.3 (6.1)	170.2 (6.0)	170.7 (6.1)	171.2 (6.1)
Body mass index, kg/m <sup>2</sup>	24.4 (3.0)	24.0 (2.7)	23.5 (2.6)	23.1 (2.8)	23.1 (3.2)
HbA1c, %	5.4 (0.4)	5.4 (0.3)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
HbA1c, mmol/mol	35.9 (3.9)	35.7 (3.7)	35.3 (3.7)	34.6 (3.7)	34.6 (3.4)
Fasting plasma glucose, mg/dL	102.3 (9.2)	101.5 (8.8)	101.0 (8.5)	99.0 (8.0)	99.8 (8.4)
Fasting plasma glucose, mmol/L	5.7 (0.5)	5.6 (0.5)	5.6 (0.5)	5.5 (0.4)	5.5 (0.5)
Weight change from 20 years of age, kg	+9.7 (9.1)	+9.0 (8.1)	+8.2 (7.9)	+7.0 (8.4)	+7.0 (20.5)
Current smoking, %	20.0	22.8	23.6	31.3	33.7
Usually drinking alcohol, %	61.7	62.3	63.8	57.3	55.2
Duration of walking per day, min	41.0 (38.3)	41.3 (41.7)	43.3 (41.5)	40.4 (35.2)	38.6 (36.0)
Physical activity of 6–7/week, %	11.2	12.0	11.9	10.4	11.6
<b>Women in urban Japan (n = 10,614)</b>	Sustained loss	Loss-gain	Stable	Gain-loss	Sustained gain
Age, years	52.4 (10.7)	51.1 (11.5)	48.9 (11.3)	45.7 (10.6)	43.5 (9.8)
Weight, kg	53.8 (8.0)	53.4 (7.8)	51.7 (7.0)	51.8 (7.1)	51.6 (7.4)
Height, cm	156.9 (5.7)	157.2 (5.9)	157.8 (5.6)	158.1 (5.5)	158.4 (5.3)
Body mass index, kg/m <sup>2</sup>	21.8 (3.0)	21.6 (3.0)	20.8 (2.7)	20.7 (2.7)	20.6 (2.8)
HbA1c, %	5.5 (0.4)	5.4 (0.4)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
HbA1c, mmol/mol	36.1 (4.1)	35.4 (3.8)	35.0 (3.8)	34.4 (3.6)	34.0 (3.7)
Fasting plasma glucose, mg/dL	96.5 (8.9)	95.7 (8.1)	94.6 (8.0)	93.2 (7.3)	92.8 (7.3)

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Fasting plasma glucose, mmol/L	5.4 (0.5)	5.3 (0.4)	5.3 (0.4)	5.2 (0.4)	5.2 (1.4)
Weight change from 20 years of age, kg	+4.1 (7.4)	+3.8 (7.3)	+2.4 (7.1)	+3.6 (7.1)	+2.2 (7.5)
Current smoking, %	6.6	6.7	5.7	9.9	11.8
Usually drinking alcohol, %	23.7	26.7	27.3	29.4	28.3
Duration of walking per day, min	42.9 (49.4)	41.2 (49.8)	42.3 (40.9)	41.5 (40.5)	43.8 (51.9)
Physical activity of 6–7/week, %	12.1	10.6	11.3	8.6	8.8
<b>Men in rural Japan (n = 4,818)</b>	<b>Sustained loss</b>	<b>Loss-gain</b>	<b>Stable</b>	<b>Gain-loss</b>	<b>Sustained gain</b>
Age, years	53.5 (10.3)	51.7 (9.8)	52.3 (10.1)	49.2 (10.1)	48.3 (10.5)
Weight, kg	67.2 (9.0)	66.2 (8.7)	66.0 (9.1)	64.7 (8.6)	64.3 (9.9)
Height, cm	167.5 (6.2)	168.0 (6.0)	167.8 (6.2)	168.5 (6.2)	168.8 (6.5)
Body mass index, kg/m <sup>2</sup>	23.9 (2.6)	23.4 (2.6)	23.4 (2.7)	22.8 (2.5)	22.5 (2.9)
HbA1c, %	5.3 (0.4)	5.3 (0.4)	5.3 (0.3)	5.2 (0.3)	5.2 (0.3)
HbA1c, mmol/mol	34.7 (3.9)	34.6 (3.9)	34.3 (3.7)	33.9 (3.8)	33.8 (3.5)
Fasting plasma glucose, mg/dL	97.5 (9.2)	96.4 (9.0)	96.9 (9.1)	95.1 (8.9)	95.1 (8.5)
Fasting plasma glucose, mmol/L	5.4 (0.5)	5.4 (0.5)	5.4 (0.5)	5.3 (0.5)	5.3 (0.5)
Current smoker, %	38.5	42.7	37.7	49.3	58.5
Current drinker, %	79.5	77.5	78.4	75.7	77.5
<b>Women in rural Japan (n = 4,852)</b>	<b>Sustained loss</b>	<b>Loss-gain</b>	<b>Stable</b>	<b>Gain-loss</b>	<b>Sustained gain</b>
Age, years	54.9 (9.0)	52.8 (8.6)	53.1 (9.2)	50.7 (9.2)	48.2 (9.9)
Weight, kg	54.0 (8.1)	53.6 (7.5)	52.9 (6.9)	51.6 (7.6)	52.6 (7.8)
Height, cm	154.1 (5.6)	154.8 (5.8)	154.6 (5.4)	155.3 (5.5)	155.7 (5.6)
Body mass index, kg/m <sup>2</sup>	22.7 (3.1)	22.4 (2.8)	22.1 (2.8)	22.8 (2.9)	21.7 (3.0)
HbA1c, %	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.2 (0.3)
HbA1c, mmol/mol	34.9 (3.7)	34.6 (3.4)	34.6 (3.6)	34.0 (3.4)	33.6 (3.3)

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Fasting plasma glucose, mg/dL	94.1 (9.1)	93.0 (8.3)	93.7 (8.8)	94.0 (8.0)	91.9 (7.9)
Fasting plasma glucose, mmol/L	5.2 (0.5)	5.2 (0.5)	5.2 (0.5)	5.2 (0.4)	5.1 (0.4)
Current smoker, %	5.5	8.1	6.6	8.5	11.5
Current drinker, %	24.2	27.2	26.5	27.1	30.9

The data are presented as the mean (SD) or %.

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## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Line 1–2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Line 23–42
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	Line 55–62
Objectives	3	State specific objectives, including any prespecified hypotheses	5	Line 71–73
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	6	Line 77–78
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	Line 77–87
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6	Line 87–93
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Line 93–97
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6–7	Line 100–122
Bias	9	Describe any efforts to address potential sources of bias	5	Line 83–90
Study size	10	Explain how the study size was arrived at	8	Line 141–142, 147–148

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6–7	Line 100–122
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7–8	Line 102–103, 124–137
		(b) Describe any methods used to examine subgroups and interactions	8	Line 131–133
		(c) Explain how missing data were addressed	6	Line 89–93
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		NA
		(e) Describe any sensitivity analyses	8	Line 131–133
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Line 141–142, 147–148
		(b) Give reasons for non-participation at each stage	6	Line 92–93
		(c) Consider use of a flow diagram		NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9	Table 1
		(b) Indicate number of participants with missing data for each variable of interest		NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10–13	Table 2 and 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10–13	Table 2 and 3
		(b) Report category boundaries when continuous variables were categorized	10–13 (BMI)	Table 2 and 3
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a		

		meaningful time period		NA
Continued on next page	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14–15	Table 4
Other analyses				
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	16	Line 192–201
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19	Line 246–271
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20	Line 285–298
Generalisability	21	Discuss the generalisability (external validity) of the study results	19–20	Line 281–284
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	Line 324–326

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Weight cycling and the subsequent onset of type 2 diabetes mellitus: ten-year cohort studies in urban and rural Japan

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014684.R2
Article Type:	Research
Date Submitted by the Author:	24-Feb-2017
Complete List of Authors:	Yokomichi, Hiroshi; University of Yamanashi, Department of Health Sciences Ohde, Sachiko; St. Luke's International University, Center for Clinical Epidemiology Takahashi, Osamu; St. Luke's International University, Center for Clinical Epidemiology Mochizuki, Mie; University of Yamanashi, Department of Pediatrics Takahashi, Atsunori; University of Yamanashi, Department of Health Sciences Yoda, Yoshioki; Yamanashi Koseiren Health Care Center Tsuji, Masahiro; Yamanashi Koseiren Health Care Center Akiyama, Yuka; University of Yamanashi, Department of Health Sciences Yamagata, Zentaro; The University of Yamanashi, Interdisciplinary Graduate School of Medicine and Engineering
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Health services research, Nutrition and metabolism, Sports and exercise medicine
Keywords:	body weight changes, type 2 diabetes, body mass index, Asian, sarcopenia

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Manuscripts

1 Yokomichi H et al.

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3 1 **Weight cycling and the subsequent onset of type 2 diabetes mellitus:**  
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5 2 **ten-year cohort studies in urban and rural Japan**

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8 3 Hiroshi Yokomichi<sup>1\*</sup>, Sachiko Ohde<sup>2</sup>, Osamu Takahashi<sup>2</sup>, Mie Mochizuki<sup>3</sup>, Atsunori  
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10 4 Takahashi<sup>1</sup>, Yoshioki Yoda<sup>4</sup>, Masahiro Tsuji<sup>4</sup>, Yuka Akiyama<sup>1</sup> and Zentaro Yamagata<sup>1</sup>

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39 17 **Keywords:** body weight changes; type 2 diabetes; body mass index; Asian; sarcopenia

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3 **ABSTRACT**

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6 **Objective:** To investigate how weight cycling impacts on the risk of diabetes.

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10 **Design:** Cohort studies.

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13 **Setting:** Primary healthcare in urban and rural Japan.

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16 **Participants:** 20,708 urban and 9,670 rural residents.

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27 **Primary outcome measures:** Odds ratios (ORs) for diabetes in weight loss, loss-gain, stable,  
28 gain-loss and weight gain for 10 years. Weight gain and loss were defined as a greater than  
29  $\pm 4\%$  change from baseline weight.

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**Results:** In the urban region, the ORs relative to the stable group for the loss-gain and  
gain-loss groups were 0.63 (95% CI: 0.45–0.89) and 0.51 (95% CI: 0.32–0.82) for men and  
0.72 (95% CI: 0.39–1.34) and 1.05 (95% CI: 0.57–1.95) for women, respectively. In the rural  
region, they were 1.58 (95% CI: 0.78–3.17) and 0.44 (95% CI: 0.15–1.29) in men and 0.41  
(95% CI: 0.12–1.44) and 0.77 (95% CI: 0.28–2.14) in women, respectively. The ORs for an  
increase in weight between 5–10 kg from the age of 20 years were 1.54 (95% CI: 1.03–2.30)  
in men and 0.96 (95% CI: 0.55–1.65) in women.

**Conclusions:** In Japan, weight cycling has been associated with a significant reduction in the  
risk of diabetes for men from an urban region. However, the associations were unclear for  
women from the urban region and for men and women from the rural region. These results  
differ from those in Western studies, likely due to differences in diet, insulin secretion and  
sensitivity and weight-consciousness.

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43 **Word count: 242 words (limit: 300 words)**

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3 44 **Strengths and limitations of this study**

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6 45 ● Of men in urban Japan, weight cyclers have a lower risk of diabetes than those who  
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8 46 maintain a constant body weight.
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10 47 ● In urban and rural Japan, sustained weight gain increases the risk of diabetes.
- 11  
12 48 ● There is a dose–response relationship for both sexes between weight gain since the age  
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14 49 of 20 years and the risk of diabetes.
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16 50 ● Odds ratios may change according to the threshold of  $\pm 4\%$  weight change in 10 years.
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18 51 ● The levels of insulin secretion and sensitivity were not measured.
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3 **53 INTRODUCTION**

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6 54 Weight gain is a well-known risk factor for incidental type 2 diabetes. Research involving  
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9 55 people of Western, Oriental and African descent has quantitatively established the risks of  
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11 56 developing diabetes in relation to weight gain.<sup>1-3</sup> Researchers have also raised the question of  
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13 57 whether repeatedly gaining and losing weight (weight cycling) is an independent risk factor  
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15 58 for developing diabetes due to gaining weight. Studies on this topic are inconsistent in  
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17 59 Westerners of Europe and the United States; several prospective studies point to weight  
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19 60 cycling as a risk factor for type 2 diabetes while others do not.<sup>4-8</sup> In contrast, the risk of  
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21 61 diabetes in Asian weight cyclers has not been researched.

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25 62 Due to the preconception linking being slim to an aesthetic standard,<sup>9 10</sup> many Asian  
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27 63 women make an effort to lose weight.<sup>11 12</sup> Another group likely to try to reduce weight is  
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29 64 middle-aged Asian businesspeople who have gained weight but have few opportunities for  
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31 65 physical activity. Recent studies have demonstrated that East Asians are much more likely  
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33 66 than Westerners to develop type 2 diabetes at a lower body mass index (BMI).<sup>13</sup> As a result, it  
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35 67 may take only a small change in weight to alter the risk of diabetes for East Asians. In  
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37 68 addition, the literature indicates that in Japan, diet, physical activity, prevalence of  
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39 69 overweight individuals and aesthetic consciousness of metropolitan residents are different  
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41 70 from those of rural residents.<sup>14 15</sup> The aim of this study was to establish whether weight  
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43 71 cyclers residing in Japan were at an increased risk of diabetes. We used Japanese urban and  
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45 72 rural data to examine this clinical question in populations with varying lifestyles.

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53 **74 METHODS**

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55 **75 Study participants and measurements**

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3 76 In these cohort studies, we enrolled participants from an urban area, Tokyo Metropolis and  
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5 77 a rural area, Yamanashi Prefecture. In Tokyo, we enrolled employees of private companies  
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7 78 who underwent medical check-ups between January 2005 and December 2014 at St. Luke's  
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9 79 International Hospital. These annual medical check-ups were based on a legal obligation  
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11 80 imposed by the Industrial Safety and Health Act in Japan.<sup>16</sup> In the Yamanashi Prefecture, we  
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13 81 enrolled employees and residents who paid for a private comprehensive medical check-up  
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15 82 service between April 1999 and March 2009 at the Yamanashi Koseiren Health Care Center.  
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17 83 A subset of participants in Yamanashi used a subsidy from their employers or administrative  
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19 84 agencies to receive the private medical check-up. Thus, the participants in the urban area  
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21 85 received almost annual medical check-ups over 10 years, and those in the rural area received  
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23 86 occasional voluntary check-ups. Participants were included in the analysis if they had no  
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25 87 diagnosis of diabetes and an HbA1c less than 6.5% (48 mmol/mol) during a baseline period  
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27 88 for the first three years of the 10-year period. If they received medical check-ups two or three  
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29 89 times during the first three years, the data from the first visit were adopted for the baseline.  
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31 90 Those included were also required to undergo a medical check-up at least twice during the  
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33 91 latter seven years of the study. Hence, participants received three to eight medical check-ups  
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35 92 to categorise weight change patterns (exposure). The onset of diabetes was identified through  
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37 93 questionnaires for the diagnosis of diabetes, the commencement of diabetic therapies or  
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39 94 glycated haemoglobin (HbA1c)  $\geq$  6.5% (48 mmol/mol).<sup>17 18</sup> At the institution in Tokyo,  
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41 95 trained nurses interviewed the participants from the age of 20 years to establish their changes  
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43 96 in weight. BMI was calculated as the participant's weight in kilograms divided by the square  
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45 97 of their height in metres.  
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55 99 **Weight change categories**  
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3 100 The participants were categorised into five groups according to their patterns of weight  
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5 101 change during the 3–10 years since the baseline period (figure 1). The stable group was  
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7 102 comprised of the participants whose weight had not changed from the baseline by more than  
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9 103  $\pm 4\%$ . The sustained gain group consisted of the participants who gained more than 4% of  
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11 104 their baseline weight and did not subsequently lose this extra weight. Similarly, the sustained  
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13 105 loss group was comprised of participants who lost more than 4% of their baseline weight and  
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15 106 did not subsequently regain this weight. The gain-loss group included participants who  
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17 107 gained more than 4% of their baseline weight but brought their weight back below +4%. The  
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19 108 loss-gain group included participants who lost more than 4% of their baseline weight but  
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21 109 brought their weight back above  $-4\%$ . From the last time point of this categorisation, the  
22  
23 110 outcome of incident diabetes was measured. Therefore, the duration of observing whether the  
24  
25 111 participants developed diabetes was between one and six years among the categories. The  
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27 112 incidence of diabetes was measured after the participants were categorised, and any data  
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29 113 measured after a diagnosis of diabetes were ignored to conserve the temporality of exposure  
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31 114 to outcome for an epidemiological causation.<sup>19</sup>

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37 115 The  $\pm 4\%$  change in weight used for this categorisation was determined as approximately a  
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39 116 one-unit change for a person with a BMI of 22 kg/m<sup>2</sup>. This was based on the 2014 reference  
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41 117 mean BMIs for Japanese men and women of 23.6 kg/m<sup>2</sup> and 21.7 kg/m<sup>2</sup>, respectively.<sup>20</sup> We  
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43 118 also took into consideration the relatively short time period of ten years for the observation.  
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45 119 The gain-loss and loss-gain group of participants were the weight cyclers of interest.

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## 50 51 121 **Statistical analysis**

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55 122 The baseline characteristics recorded for the participants included age, weight, height, BMI,  
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57 123 HbA1c and fasting plasma glucose. We used univariate and multivariable logistic regressions

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3 124 to compare the risk of diabetes between the categorised groups. In the urban data of Tokyo  
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5 125 Metropolis, the covariates used for the adjustment at baseline were age, weight change from  
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7 126 20 years of age, BMI, smoking habits, alcohol consumption and physical activity. In the rural  
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9 127 data of the Yamanashi Prefecture, the available covariates for the adjustment at baseline were  
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11 128 age, BMI, smoking habit and alcohol consumption. The analyses were stratified by sex. In  
12  
13 129 addition, another focus of this study was the impact of weight cycling on incidental diabetes  
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15 130 in middle-aged individuals. Hence, for a sensitivity analysis, we restricted the analyses to a  
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17 131 middle-aged population of 45 to 64 years. All statistical analyses were performed using SAS  
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19 132 statistical software (version 9.3, SAS Institute, NC, USA). The descriptive statistics are  
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21 133 reported as the means and standard deviations (SD). All reported p values were two-sided; P  
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23 134 values of <0.05 were considered to be statistically significant.  
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## 30 **RESULTS**

### 31 **Participants**

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36 138 For the multivariable analyses of primary interest, 10,094 men and 10,614 women were  
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38 139 enrolled from Tokyo Metropolis (Table 1). The means (SDs) of the baseline characteristics  
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40 140 for the men in the urban region were as follows: age 49.6 (11.9) years, weight 68.8 (9.7) kg,  
41  
42 141 BMI 23.7 (2.8) kg/m<sup>2</sup> and HbA1c 5.4% (0.3%) (35.3 [3.7] mmol/mol). For the women in the  
43  
44 142 urban region, these values were as follows: age 48.3 (11.3) years, weight 52.3 (7.4) kg, BMI  
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46 143 21.0 (2.9) kg/m<sup>2</sup> and HbA1c 5.3% (0.4%) (35.0 [3.8] mmol/mol).  
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51 144 Table 1 also shows the baseline characteristics of 4,818 men and 4,852 women enrolled  
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53 145 from the Yamanashi Prefecture. The baseline characteristics for the men in the rural region  
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55 146 were as follows: age 51.2 (10.3) years, weight 65.7 (9.1) kg, BMI 23.2 (2.7) kg/m<sup>2</sup> and  
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57 147 HbA1c 5.3% (0.3%) (34.3 [3.8] mmol/L). For the women in the rural area, the values were as  
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3 148 follows: age 52.1 (9.4) years, weight 53.1 (7.5) kg, BMI 22.1 (2.9) kg/m<sup>2</sup> and HbA1c 5.3%  
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5 149 (0.3%) (34.4 [3.5] mmol/L).  
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9 **Table 1. Baseline characteristics of the participants from urban (Tokyo Metropolis) and**  
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11 **rural (Yamanashi Prefecture) regions of Japan.**  
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Characteristics, mean (standard deviation)	Men	Women
<b>Urban region</b>		
No.	10,094	10,614
Age, years	49.6 (11.9)	48.3 (11.3)
Weight, kg	68.8 (9.7)	52.3 (7.4)
Height, cm	170.4 (6.1)	157.7 (5.6)
Body mass index, kg/m <sup>2</sup>	23.7 (2.8)	21.0 (2.9)
HbA1c, %	5.4 (0.3)	5.3 (0.4)
(HbA1c, mmol/mol)	35.3 (3.7)	35.0 (3.8)
Fasting plasma glucose, mg/dL	100.8 (8.6)	94.5 (8.0)
(Fasting plasma glucose, mmol/L)	5.6 (0.5)	5.2 (0.4)
<b>Rural region</b>		
No.	4,818	4,852
Age, years	51.2 (10.3)	52.1 (9.4)
Weight, kg	65.7 (9.1)	53.1 (7.5)
Height, cm	168.1 (6.2)	154.8 (5.6)
Body mass index, kg/m <sup>2</sup>	23.2 (2.7)	22.1 (2.9)
HbA1c, %	5.3 (0.3)	5.3 (0.3)
(HbA1c, mmol/mol)	34.3 (3.8)	34.4 (3.5)
Fasting plasma glucose, mg/dL	96.3 (9.0)	93.2 (8.5)
(Fasting plasma glucose, mmol/L)	5.3 (0.5)	5.2 (0.5)

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153 **Risk of diabetes in urban and rural Japan**

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154 Tables 2 and 3 present the incidence of diabetes and the odds ratios (ORs) for each  
155 explanatory variable in the urban and rural regions, respectively. For men in the urban region,  
156 means (SDs) of follow-up duration and numbers of measurements were 7.4 (1.9) years and  
157 5.4 (1.6) in the sustained gain group, 8.2 (1.2) years and 5.7 (1.4) in the gain-loss group, 7.9  
158 (1.7) years and 4.9 (1.7) in the stable group, 8.2 (1.2) years and 5.8 (1.4) in the loss-gain  
159 group and 7.7 (1.9) years and 5.8 (1.6) in the sustained loss group, respectively. The  
160 corresponding values for women in the urban region were 7.5 (1.9) years and 5.6 (1.6) in the  
161 sustained gain group, 8.2 (1.1) years and 5.9 (1.4) in the gain-loss group, 7.9 (1.6) years and  
162 5.0 (1.7) in the stable group, 8.2 (1.2) years and 5.9 (1.4) in the loss-gain group and 7.9 (1.7)  
163 years and 6.0 (1.5) in the sustained loss group, respectively. For men in the rural region,  
164 means (SDs) of follow-up duration and numbers of measurement were 7.4 (1.6) years and 5.4  
165 (1.6) in the sustained gain group, 7.8 (1.4) years and 6.1 (1.3) in the gain-loss group, 7.1 (1.9)  
166 years and 5.2 (1.6) in the stable group, 7.9 (1.4) years and 6.2 (1.2) in the loss-gain group and  
167 7.3 (1.7) years and 5.2 (1.6) in the sustained loss group, respectively. The corresponding  
168 values for women in the rural region were 7.3 (1.6) years and 5.1 (1.6) in the sustained gain  
169 group, 7.9 (1.4) years and 6.0 (1.3) in the gain-loss group, 7.0 (1.8) years and 5.0 (1.6) in the  
170 stable group, 7.9 (1.3) years and 6.1 (1.3) in the loss-gain group and 7.4 (1.7) years and 5.4  
171 (1.5) in the sustained loss group, respectively. For the men in the urban region, the adjusted  
172 ORs (95% confidence intervals [95% CIs]) compared to the stable group were 3.07 (2.15–  
173 4.39) in the sustained gain group, 0.51 (0.32–0.82) in the gain-loss group, 0.63 (0.45–0.89) in  
174 the loss-gain group and 1.11 (0.77–1.59) in the sustained loss group. For the women in the  
175 urban region, the adjusted ORs compared to the stable group were 7.00 (4.11–11.94) in the  
176 sustained gain group, 1.05 (0.57–1.95) in the gain-loss group, 0.72 (0.39–1.34) in the  
177 loss-gain group and 1.48 (0.80–2.74) in the sustained loss group. For the men in the rural  
178 region, the adjusted ORs were 3.15 (1.70–5.83) in the sustained gain group, 0.44 (0.15–1.29)

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179 in the gain-loss group, 1.58 (0.78–3.17) in the loss-gain group and 0.36 (0.12–1.05) in the  
 180 sustained loss group. For the women in the rural region, the adjusted ORs were 1.43 (0.59–  
 181 3.48) in the sustained gain group, 0.77 (0.28–2.14) in the gain-loss group, 0.41 (0.12–1.44) in  
 182 the loss-gain group and 0.32 (0.09–1.10) in the sustained loss group.

183 **Table 2. The incidence and odds ratios (95% CIs) of diabetes related to patterns of**  
 184 **weight change over 10 years in residents of urban Japan**

Exposure variables		Acquired DM / No. of subjects (incidence, %)	Crude	Multivariate
<b>Men (No. For multivariate analysis =10,094)</b>				
Baseline age	Per 10 years	—	1.44 (1.33–1.55)	1.44 (1.29–1.61)
	< –5	7/1438 (0.5)	2.18 (1.14–4.18)	1.68 (0.75–3.80)
Weight change from 20 years of age, kg	–5 to +5	73/10646 (0.7)	Ref	Ref
	+5 to +10	31/3200 (1.0)	1.98 (1.45–2.72)	1.54 (1.03–2.30)
	> +10	78/2166 (3.6)	3.37 (2.54–4.48)	2.08 (1.40–3.10)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	6/387 (1.6)	1.35 (0.57–3.16)	0.88 (0.29–2.70)
	18.5–22	49/4236 (1.2)	Ref	Ref
	22–25	168/7220 (2.3)	2.04 (1.48–2.89)	1.73 (1.14–2.63)
	> 25	190/4699 (4.0)	3.60 (2.62–4.94)	2.52 (1.60–3.95)
Weight change pattern over 10 years	Sustained loss	66/1903 (3.5)	1.39 (1.03–1.87)	1.11 (0.77–1.59)
	Loss–gain	87/4644 (1.9)	0.74 (0.56–0.97)	0.63 (0.45–0.89)
	Stable	142/5621 (2.5)	Ref	Ref
	Gain–loss	38/3063 (1.2)	0.49 (0.34–0.70)	0.51 (0.32–0.82)
	Sustained gain	80/1311 (6.1)	2.51 (1.89–3.32)	3.07 (2.15–4.39)
Smoking	None	123/6385 (1.9)	Ref	Ref
	Ex-smoker	150/5940 (2.5)	1.32 (1.04–1.68)	0.97 (0.71–1.31)
	Current smoker	140/4217 (3.3)	1.75 (1.37–2.23)	1.73 (1.25–2.34)
Alcohol drinking	None	69/2250 (3.1)	Ref	Ref
	Sometimes	48/1667 (2.9)	0.94 (0.65–1.36)	0.96 (0.66–1.40)
	Usually	156/6177 (2.5)	0.82 (0.61–1.09)	0.78 (0.58–1.05)

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Duration of walking per day	Per 30 min	—	0.996 (0.92–1.08)	1.01 (0.92–1.11)
Physical activity	0–1/week	85/3282 (2.6)	Ref	Ref
	1–2/week	108/4105 (2.6)	1.02 (0.76–1.36)	1.02 (0.76–1.36)
	3–5/week	43/1541 (2.8)	1.08 (0.74–1.57)	0.98 (0.67–1.45)
	6–7/week	37/1166 (3.2)	1.23 (0.83–1.82)	1.06 (0.69–1.62)
<b>Women (No. for multivariate analysis = 10,614)</b>				
Baseline age	Per 10 years	—	1.66 (1.48–1.87)	1.78 (1.50–2.12)
Weight change from 20 years of age, kg	< –5	11/439 (2.5)	0.71 (0.33–1.54)	0.48 (0.18–1.25)
	–5 to +5	61/5243 (1.2)	Ref	Ref
	+5 to +10	109/4779 (2.3)	1.42 (0.93–2.16)	0.96 (0.55–1.65)
	> +10	232/6081 (3.8)	5.41 (3.92–7.47)	2.10 (1.20–3.67)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	20/2916 (0.7)	1.24 (0.74–2.08)	1.47 (0.76–2.86)
	18.5–22	52/9388 (0.6)	Ref	Ref
	22–25	60/3676 (1.6)	2.98 (2.05–4.33)	2.01 (1.21–3.34)
	> 25	57/1470 (3.9)	7.24 (4.95–10.59)	2.91 (1.53–5.52)
Weight change pattern over 10 years	Sustained loss	24/1661 (1.4)	2.11 (1.25–3.54)	1.48 (0.80–2.74)
	Loss–gain	32/4022 (0.7)	1.15 (0.72–1.86)	0.72 (0.39–1.34)
	Stable	36/5212 (1.3)	Ref	Ref
	Gain–loss	30/4630 (0.6)	0.94 (0.58–1.53)	1.05 (0.57–1.95)
	Sustained gain	67/1925 (3.5)	5.19 (3.45–7.80)	7.00 (4.11–11.94)
Smoking	None	156/14,194 (1.1)	Ref	Ref
	Ex-smoker	17/1789 (1.0)	0.86 (0.52–1.143)	0.85 (0.45–1.61)
	Current smoker	16/1467 (1.1)	0.99 (0.59–1.67)	1.20 (0.63–2.32)
Alcohol drinking	None	78/5669 (1.4)	Ref	Ref
	Sometimes	20/2035 (1.0)	0.71 (0.43–1.17)	0.91 (0.55–1.52)
	Usually	27/2910 (0.9)	0.67 (0.43–1.04)	0.95 (0.60–1.51)
Duration of walking per day	Per 30 min	—	1.01 (0.93–1.11)	1.01 (0.90–1.13)
Physical activity	0–1/week	37/3894 (1.0)	Ref	Ref
	1–2/week	42/3760 (1.1)	1.18 (0.76–1.84)	1.11 (0.70–1.75)
	3–5/week	27/1874 (1.4)	1.52 (0.93–2.52)	1.14 (0.67–1.94)
	6–7/week	19/1086 (1.7)	1.86 (1.06–3.24)	1.43 (0.79–2.60)

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185 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

186 **Table 3. The incidence and odds ratios (95% CIs) of diabetes related to patterns of**  
 187 **weight change over 10 years in residents of rural Japan**

Exposure variables		Acquired DM / No. of subjects (incidence, %)	Crude	Multivariate
<b>Men (No. for multivariate analysis = 4818)</b>				
Baseline age	Per 10 years	—	1.36 (1.08–1.72)	1.60 (1.24–2.05)
	< 18.5	0/167 (0)	—	—
Baseline BMI, kg/m <sup>2</sup>	18.5–22	10/1425 (0.7)	Ref	Ref
	22–25	21/2079 (1.0)	1.44 (0.68–3.08)	1.69 (0.79–3.63)
	> 25	35/1148 (3.1)	4.45 (2.19–9.03)	5.81 (2.82–11.97)
Weight change pattern over 10 years	Sustained loss	4/725 (0.6)	0.43 (0.15–1.25)	0.36 (0.12–1.05)
	Loss–gain	13/681 (1.9)	1.50 (0.75–3.00)	1.58 (0.78–3.17)
	Stable	22/1719 (1.3)	Ref	Ref
	Gain–loss	4/916 (0.4)	0.34 (0.12–0.99)	0.44 (0.15–1.29)
	Sustained gain	23/778 (3.0)	2.35 (1.30–4.24)	3.15 (1.70–5.83)
Smoking	None	23/1695 (1.4)	Ref	Ref
	Ex-smoker	8/998 (0.8)	0.59 (0.26–1.32)	0.72 (0.32–1.64)
	Current smoker	35/2126 (1.7)	1.22 (0.72–2.07)	1.50 (0.85–2.62)
Drinking	None	11/1071 (1.0)	Ref	Ref
	Drinker	55/3748 (1.5)	1.44 (0.75–2.75)	1.52 (0.79–2.94)
<b>Women (No. for multivariate analysis = 4852)</b>				
Baseline age	Per 10 years	—	1.43 (0.99–2.06)	1.23 (0.83–1.84)
	< 18.5	0/411 (0)	—	—
Baseline BMI, kg/m <sup>2</sup>	18.5–22	7/2135 (0.3)	Ref	Ref
	22–25	14/1563 (0.9)	2.75 (1.11–6.82)	2.69 (1.07–6.75)
	> 25	13/744 (1.8)	5.41 (2.15– 13.60)	5.29 (2.07–13.51)
Weight change pattern over 10 years	Sustained loss	3/863 (0.3)	0.37 (0.11–1.29)	0.32 (0.09–1.10)
	Loss–gain	3/757 (0.4)	0.42 (0.12–1.47)	0.41 (0.12–1.44)
	Stable	15/1615 (0.9)	Ref	Ref
	Gain–loss	5/827 (0.6)	0.65 (0.24–1.79)	0.77 (0.28–2.14)

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	Sustained gain	8/791 (1.0)	1.09 (0.46–2.58)	1.43 (0.59–3.48)
	None	2/646 (0.3)	Ref	Ref
Smoking	Ex-smoker	29/3822 (0.8)	2.45 (0.58–10.31)	2.19 (0.52–9.26)
	Current smoker	3/375 (0.8)	2.60 (0.43–15.60)	3.33 (0.55–20.28)
Drinking	None	31/3542 (0.9)	Ref	Ref
	Drinker	3/1311 (0.2)	0.26 (0.08–0.85)	0.29 (0.09–0.95)

188 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

189

190 Table 4 shows the risk of diabetes risk due to weight cycling in the middle-aged population.

191 The ORs (95% CIs) for incidental diabetes were 0.57 (0.32–1.01) in the gain-loss group and

192 0.74 (0.49–1.11) in the loss-gain group among men living in the urban area. The

193 corresponding ORs (95% CIs) were 0.80 (0.36–1.77) and 0.76 (0.37–1.57), respectively

194 among women living in the urban area. The ORs were 0.58 (0.19–1.77) and 1.76 (0.80–3.87),

195 respectively among men living in rural area; 0.82 (0.26–2.62) and 0.54 (0.15–1.94),

196 respectively among the women living in the rural area.

197

198 **Table 4. The incidence and odds ratios of diabetes related to patterns of weight change over 10 years**  
 199 **in middle-aged residents (45–64 years) in Japan**

Exposure variables	Acquired DM / No. of subjects (incidence, %)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
<b>Urban middle-aged men (No. for multivariate analysis =4,882)</b>			
Weight change pattern over 10 years	Sustained loss	35/981 (3.6)	1.04 (0.65–1.67)
	Loss-gain	62/2203 (2.8)	0.79 (0.53–1.18)
	Stable	100/2749 (3.6)	Ref
	Gain-loss	26/1098 (2.4)	0.56 (0.32–0.999)
	Sustained gain	50/489 (10.2)	3.09 (2.00–4.76)

**Urban middle-aged women (No. for multivariate analysis = 5,053)**

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2					
3		Sustained loss	15/994 (1.5)	1.30 (0.62–2.73)	1.13 (0.53–2.41)
4		Loss-gain	20/1992 (1.0)	0.87 (0.43–1.77)	0.76 (0.37–1.57)
5	Weight change pattern over 10 years	Stable	24/2285 (1.1)	Ref	Ref
6		Gain-loss	17/1642 (1.0)	0.74 (0.34–1.62)	0.80 (0.36–1.77)
7		Sustained gain	40/603 (6.6)	5.62 (3.05–10.37)	6.97 (3.67–13.25)
8					
9	<b>Rural middle-aged men (No. for multivariate analysis =2,937)</b>				
10					
11		Sustained loss	3/447 (0.7)	0.48 (0.14–1.66)	0.42 (0.12–1.47)
12		Loss-gain	11/449 (2.5)	1.78 (0.81–3.91)	1.76 (0.80–3.87)
13	Weight change pattern over 10 years	Stable	15/1078 (1.4)	Ref	Ref
14		Gain-loss	4/546 (0.7)	0.52 (0.17–1.58)	0.58 (0.19–1.77)
15		Sustained gain	12/417 (2.9)	2.10 (0.98–4.53)	2.48 (1.12–5.49)
16					
17	<b>Rural middle-aged women (No. for multivariate analysis = 3,347)</b>				
18					
19		Sustained loss	1/638 (0.2)	0.16 (0.02–1.25)	0.14 (0.02–1.01)
20		Loss-gain	3/579 (0.5)	0.54 (0.15–1.92)	0.54 (0.15–1.94)
21	Weight change pattern over 10 years	Stable	11/1140 (1.0)	Ref	Ref
22		Gain-loss	4/558 (0.7)	0.74 (0.24–2.34)	0.82 (0.26–2.62)
23		Sustained gain	5/432 (1.2)	1.20 (0.42–3.48)	1.30 (0.44–3.84)
24					

200 Multivariable logistic regression calculated odds ratios with an adjustment for baseline age and BMI, weight  
 201 change from 20 years of age, smoking and drinking habits, duration of walking per day and physical activity  
 202 per week in the urban data. The baseline age and BMI and smoking and drinking habits in the rural data.

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204 **DISCUSSION**

205 The data for the Japanese urban region suggest that the risk of diabetes in male weight  
206 cyclers was significantly lower than that of those who maintained a stable weight (table  
207 2). The diabetes risk for female weight cyclers in the urban region was non-significantly  
208 lower than or similar to the risk for those maintaining a stable weight. The data for  
209 Japanese men and women residing in the rural region also suggest no risk and a  
210 non-significantly lower risk, respectively, of diabetes with weight cycling compared  
211 with maintaining a stable weight (table 3). These results are reinforced by a sensitivity  
212 analysis with a restriction on middle-aged individuals, yielding almost same ORs  
213 without statistical significance (table 4) as those of the entire population.

214 These observations are not consistent with those from previous studies of Western  
215 populations, which showed that weight cycling significantly or non-significantly  
216 increased the risk of diabetes for point estimates. In the Framingham Heart Study,  
217 approximately 1 kg/m<sup>2</sup> of weight cycling in middle-aged Americans carried a hazard  
218 ratio of 1.1 (95%CI: 0.8–1.5) for the risk of diabetes after adjusting for sex and BMI at  
219 25 years of age.<sup>4</sup> In the American middle-aged women of the National Health and  
220 Nutrition Examination Survey, weight cycling of 4.5–9.1 kg and 9.1–22.2 kg with an  
221 intentional weight loss three or more times in four years carried ORs for the risk of  
222 diabetes of 1.11 (95%CI: 0.89–1.37) and 1.39 (95%CI: 0.90–2.13), respectively.<sup>5</sup> A  
223 study from a cohort of medical students at the Johns Hopkins University School of  
224 Medicine reported that the highest quartile of BMI variability for ages between 25 and  
225 45 years had an OR of 2.1 (95%CI: 1.0–4.6) for the risk of diabetes after 50 years,  
226 compared with the other three lower quartiles.<sup>21</sup> In a large German cohort, weight

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227 cycling of  $\geq 1.5$  kg/year was significantly associated with an adjusted hazard ratio of  
228 1.34.<sup>6</sup>

229 The disparity between the results of this study and the Western studies may be due to  
230 ethnic differences in diet,<sup>22</sup> the capacity to gain weight<sup>23</sup> and self-consciousness about  
231 body weight.<sup>24</sup> Further research is required to explore why the relationship between  
232 weight cycling and risk of diabetes is inversed between Western and East Asian  
233 populations. The reason may be attributable to different motivations to lose weight in  
234 the context of different diet cultures and body self-consciousness.<sup>25</sup> The East Asians  
235 who try to lose weight may be particularly those who are relatively concerned about the  
236 poor health outcomes of being overweight. Westerners described in the study cohorts  
237 who tried to lose weight may, in an extreme expression, have been those who lost and  
238 regained a great deal of weight and potentially ran the risk of poor health outcomes.

239 From the data from the urban region, a weight increase of more than +5 kg above the  
240 participant's weight at the age of 20 years increased the risk of developing diabetes with  
241 a dose-response relationship in both men and women (table 2). Furthermore, in both  
242 sexes, an increase in weight of more than +10 kg above that when aged 20 years more  
243 than doubles the risk of diabetes, with statistical significance, compared to the risk for  
244 those who maintained their weight within  $\pm 5$  kg of their weight when aged 20 years.  
245 These results agree with the study involving a US cohort, which reported a relative risk  
246 of 3.2 (95%CI: 1.4–7.4) for the highest quartile of an increase in BMI from 25 to 45  
247 years of age in comparison with the other three lower quartiles.<sup>21</sup> A dose-response  
248 relationship of weight change from that aged 20 years to the risk of diabetes occurred in  
249 the Japanese women residing in the urban region, with ORs of 0.48 (95%CI: 0.18–1.25)

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5 250 for a change less than 5 kg, 0.96 (95%CI: 0.55–1.65) for an increase of between 5 and  
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7 251 10 kg and 2.10 (95%CI: 1.20–3.67) for an increase greater than 10 kg (table 2). In  
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10 252 contrast, the Japanese men who had lost 5 kg or more of body weight between the age  
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12 253 of 20 years and early middle age had an OR of 1.68 (95%CI: 0.75–3.80). This  
13  
14 254 paradoxically increased OR was most likely due to the small number of participants  
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16 255 (seven) who developed diabetes among a weight loss group of 1438 people.  
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20 256 This study had several limitations. The first of these was the threshold of  $\pm 4\%$  weight  
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22 257 change in 10 years. This threshold referred to a study from United Kingdom on the  
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24 258 association between weight change and the risk of diabetes.<sup>26</sup> The threshold of a  $\pm 4\%$   
25  
26 259 weight change was calculated as approximately 1 BMI unit in Japanese people with a  
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28 260 mean BMI of 23 kg/m<sup>2</sup>. However, the threshold for categorisation of weight cycling  
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30 261 should vary according to mean BMIs in different ethnicities, in which people have  
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32 262 different insulin sensitivities.<sup>13 27</sup> Second, we did not evaluate insulin sensitivity.  
33  
34 263 Measuring fasting plasma glucose and insulin concentration to calculate HOMA-IR,<sup>28</sup>  
35  
36 264 an index of insulin resistance, would have allowed us to assess the association between  
37  
38 265 weight cycling and the physiological hazard of diabetes. Third, the weight changes  
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40 266 recorded in the rural region may be misclassified due to missing data for the years when  
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42 267 participants did not undergo the health examination. However, such misclassification  
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44 268 would bias the ORs to the null hypothesis, and we believe that such a bias would not  
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46 269 change the conclusions for the rural region. Fourth, we could not examine whether the  
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48 270 weight cycling was intentional; however, we consider that a subset of unintentional  
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50 271 weight loss could be attributed to metabolic diseases, and patients with such diseases  
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53 272 could not usually regain the weight within a short duration. Fifth, the follow-up duration  
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5 273 and the numbers of weight measurements vary among the groups of weight change  
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7 274 patterns. However, because perfect categorisation of changing weight over time would  
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9 275 be impossible, we think that this study design could answer the study question. Sixth,  
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11 276 the urban data for the weight at 20 years of age were derived from the participants'  
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13 277 memory. Thus, recall bias could have existed in the results. Seventh, a subset of the  
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15 278 diagnoses in this study were not made by physicians but via an epidemiological  
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17 279 criteria.<sup>17</sup> However, most observational studies by nature rely on epidemiological  
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19 280 criteria for detecting diabetes, and the use of a consistent diagnostic criterion can allow  
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21 281 researchers to compare the risk of diabetes onset between the reference group and that  
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23 282 of interest. Last, this study lacks the information pertaining to lifestyle, including diet,  
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25 283 marriage status, job type and owning a car, that may have partly explain the association  
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27 284 between weight cycling and incident diabetes.  
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33 285 The present study also has several strengths. First, to the best of our knowledge, this  
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35 286 is the first study to explore the relationship between weight cycling and the risk of  
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37 287 diabetes in Asians. Since the relationship in this study was almost opposite to that of  
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39 288 Americans, further research in East Asians is necessary to confirm this relationship.  
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41 289 Next, this study was conducted in two differently characterised populations (urban and  
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43 290 rural residents). The ORs of the risk of diabetes were 1.05 (95%CI: 0.57–1.95) in the  
44  
45 291 weight gain-loss pattern of the urban resident women (table 2) and 1.58 (95%CI: 0.78–  
46  
47 292 3.17) in weight loss-gain pattern of the rural resident men (table 3). However, all other  
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49 293 weight cycling patterns for both sexes in the urban and rural regions were negatively  
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51 294 correlated with the risk of diabetes with and without statistical significance (tables 2 and  
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53 295 3). Third, the number of participants in both sexes were approximately 10,000 in the  
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5 296 urban region and approximately 5,000 in the rural region. Since the present study  
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7 297 included a large number of participants from both urban and rural Japan, Japanese and  
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10 298 East Asian weight cyclers could refer to its results.

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13 299 This study could contribute to aiding public health practitioners and on-site clinical  
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15 300 professionals prevent diabetes in the general population. A sustained weight gain greater  
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17 301 than 4% over ten years in middle age (table 4) and more than 5 kg of additional weight  
18  
19 302 gain since the age of 20 years (table 2) both may carry an increased risk of diabetes for  
20  
21 303 both sexes. Since middle-aged people can easily undergo such a small weight gain over  
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23 304 the short or long term, non-diabetic people within the normal BMI range should be  
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25 305 cautious about the risks resulting from even such a slight weight gain through their  
26  
27 306 lifetime. An interventional study indicated that weight loss ( $-1.8 \text{ kg/m}^2$  of BMI in a diet  
28  
29 307 intervention group and  $-3.3 \text{ kg/m}^2$  of BMI in a diet-and-exercise intervention group)  
30  
31 308 improved insulin sensitivity in Japanese patients with obesity and type 2 diabetes.<sup>29</sup>  
32  
33 309 Improved insulin sensitivity was also observed in Americans who maintained their  
34  
35 310 weight with treadmill-based exercise and no alteration in their diet.<sup>30</sup> In addition, studies  
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37 311 have demonstrated that building muscle through exercising without changing weight  
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39 312 improves insulin sensitivity.<sup>31</sup>

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44 313 While not statistically significant, two profiles of weight cycling pattern in the  
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46 314 present study resulted in an increased risk of diabetes whereas the risk decreased for the  
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48 315 other six profiles (tables 2 and 3). Since better insulin sensitivity directly leads to a  
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50 316 decreased risk of diabetes, the results may be due to the differences in how the  
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52 317 participants lost or gained weight (i.e. whether they lost or gained fat or muscle mass).  
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54 318 Recent studies have indicated that sarcopenia, the loss of skeletal muscle alone or with  
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5 319 increased fat mass in ageing, is a leading cause of death in old age.<sup>32</sup> The results of the  
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7 320 present study, in the context of previous studies, suggest that over both the short- and  
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10 321 long-term, people might reduce their risk of diabetes by losing fat and maintaining  
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12 322 muscle mass.

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18 324 **CONCLUSIONS**

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22 325 In men in an urban region of Japan, weight cycling was associated with a significant  
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24 326 reduction in the risk of diabetes; however, a clear association was not observed in either  
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26 327 women of the urban region or in men and women of a rural region. The results were  
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28 328 different than those recorded in Western countries and may be attributed to differences  
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30 329 in diet, endocrinological capacity to gain weight and weight-consciousness. In addition,  
31  
32 330 the risk of diabetes increases linearly with weight gain from the age of 20 years in  
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34 331 Japanese urban men and women. A study that includes the measurement of insulin  
35  
36 332 sensitivity is necessary to confirm the present results and to improve the understanding  
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38 333 of the risks for East Asian weight cyclers.

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42 334 **(3,508 words; limit of 4,000 words)**

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5 335 **Acknowledgments** We thank all participants in this study and staff at the St. Luke's  
6  
7 336 International Hospital and the Yamanashi Koseiren Health Care Center for their support,  
8  
9 337 which made this study possible.  
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13 338 **Competing interests** None declared.  
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15  
16 339 **Funding** This work was supported by the Ministry of Education, Culture, Sports,  
17  
18 340 Science and Technology of Japan (MEXT) (KAKENHI grant number: JP15K08730 and  
19  
20 341 JP15K15221). The funder had no role in study design, analysis, decision to publish or  
21  
22 342 preparation of the manuscript.  
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25  
26 343 **Contributors** ZY, YY, MT and OT: setting up the study and data collection. HY, ZY,  
27  
28 344 MM and AT: designing the study. HY and AT: data analysis. HY: writing and revising  
29  
30 345 the draft. ZY, SO, MM, YA and HY: development of the discussion section. All authors  
31  
32 346 read and approved the final manuscript.  
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36 347 **Ethics approval** The ethics committee of the School of Medicine, University of  
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38 348 Yamanashi (approval number: H27-1417).  
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42 349 **Data sharing statement** No additional data are available.  
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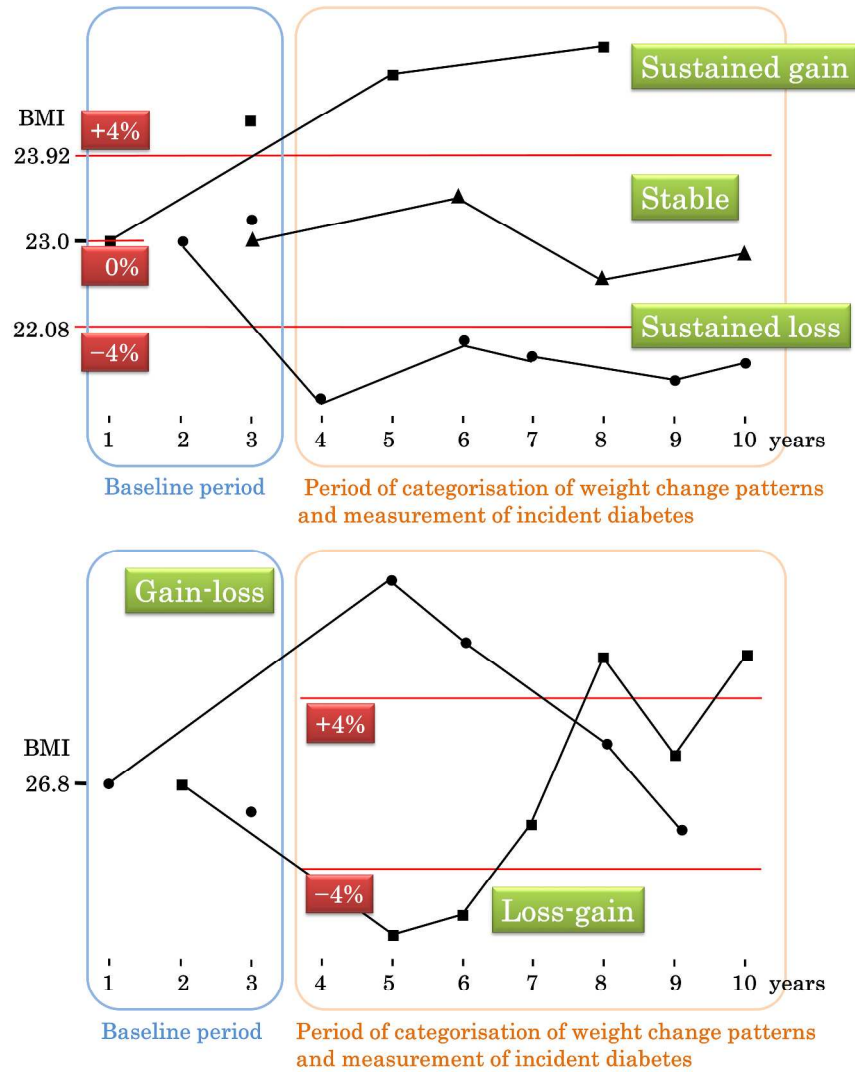
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440 **Figure 1. Scheme of how participants were categorised into the five**  
441 **weight change patterns**

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For peer review only

## Categorisation of weight change patterns



Scheme of how participants were categorised into the five weight change patterns  
figure 1

339x454mm (300 x 300 DPI)



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**Supplementary. Baseline characteristics among groups of weight change patterns over 10 years**

<b>Men in urban Japan (n = 10,094)</b>	Sustained loss	Loss-gain	Stable	Gain-loss	Sustained gain
Age, years	52.3 (12.2)	51.2 (12.0)	50.3 (11.3)	46.0 (11.4)	44.9 (11.3)
Weight, kg	70.8 (10.4)	69.8 (9.5)	68.3 (9.0)	67.3 (9.5)	67.8 (10.8)
Height, cm	170.1 (6.2)	170.3 (6.1)	170.2 (6.0)	170.7 (6.1)	171.2 (6.1)
Body mass index, kg/m <sup>2</sup>	24.4 (3.0)	24.0 (2.7)	23.5 (2.6)	23.1 (2.8)	23.1 (3.2)
HbA1c, %	5.4 (0.4)	5.4 (0.3)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
HbA1c, mmol/mol	35.9 (3.9)	35.7 (3.7)	35.3 (3.7)	34.6 (3.7)	34.6 (3.4)
Fasting plasma glucose, mg/dL	102.3 (9.2)	101.5 (8.8)	101.0 (8.5)	99.0 (8.0)	99.8 (8.4)
Fasting plasma glucose, mmol/L	5.7 (0.5)	5.6 (0.5)	5.6 (0.5)	5.5 (0.4)	5.5 (0.5)
Weight change from 20 years of age, kg	+9.7 (9.1)	+9.0 (8.1)	+8.2 (7.9)	+7.0 (8.4)	+7.0 (20.5)
Current smoking, %	20.0	22.8	23.6	31.3	33.7
Usually drinking alcohol, %	61.7	62.3	63.8	57.3	55.2
Duration of walking per day, min	41.0 (38.3)	41.3 (41.7)	43.3 (41.5)	40.4 (35.2)	38.6 (36.0)
Physical activity of 6–7/week, %	11.2	12.0	11.9	10.4	11.6
<b>Women in urban Japan (n = 10,614)</b>	Sustained loss	Loss-gain	Stable	Gain-loss	Sustained gain
Age, years	52.4 (10.7)	51.1 (11.5)	48.9 (11.3)	45.7 (10.6)	43.5 (9.8)
Weight, kg	53.8 (8.0)	53.4 (7.8)	51.7 (7.0)	51.8 (7.1)	51.6 (7.4)
Height, cm	156.9 (5.7)	157.2 (5.9)	157.8 (5.6)	158.1 (5.5)	158.4 (5.3)
Body mass index, kg/m <sup>2</sup>	21.8 (3.0)	21.6 (3.0)	20.8 (2.7)	20.7 (2.7)	20.6 (2.8)
HbA1c, %	5.5 (0.4)	5.4 (0.4)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
HbA1c, mmol/mol	36.1 (4.1)	35.4 (3.8)	35.0 (3.8)	34.4 (3.6)	34.0 (3.7)
Fasting plasma glucose, mg/dL	96.5 (8.9)	95.7 (8.1)	94.6 (8.0)	93.2 (7.3)	92.8 (7.3)

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Fasting plasma glucose, mmol/L	5.4 (0.5)	5.3 (0.4)	5.3 (0.4)	5.2 (0.4)	5.2 (1.4)
Weight change from 20 years of age, kg	+4.1 (7.4)	+3.8 (7.3)	+2.4 (7.1)	+3.6 (7.1)	+2.2 (7.5)
Current smoking, %	6.6	6.7	5.7	9.9	11.8
Usually drinking alcohol, %	23.7	26.7	27.3	29.4	28.3
Duration of walking per day, min	42.9 (49.4)	41.2 (49.8)	42.3 (40.9)	41.5 (40.5)	43.8 (51.9)
Physical activity of 6–7/week, %	12.1	10.6	11.3	8.6	8.8
<b>Men in rural Japan (n = 4,818)</b>	<b>Sustained loss</b>	<b>Loss-gain</b>	<b>Stable</b>	<b>Gain-loss</b>	<b>Sustained gain</b>
Age, years	53.5 (10.3)	51.7 (9.8)	52.3 (10.1)	49.2 (10.1)	48.3 (10.5)
Weight, kg	67.2 (9.0)	66.2 (8.7)	66.0 (9.1)	64.7 (8.6)	64.3 (9.9)
Height, cm	167.5 (6.2)	168.0 (6.0)	167.8 (6.2)	168.5 (6.2)	168.8 (6.5)
Body mass index, kg/m <sup>2</sup>	23.9 (2.6)	23.4 (2.6)	23.4 (2.7)	22.8 (2.5)	22.5 (2.9)
HbA1c, %	5.3 (0.4)	5.3 (0.4)	5.3 (0.3)	5.2 (0.3)	5.2 (0.3)
HbA1c, mmol/mol	34.7 (3.9)	34.6 (3.9)	34.3 (3.7)	33.9 (3.8)	33.8 (3.5)
Fasting plasma glucose, mg/dL	97.5 (9.2)	96.4 (9.0)	96.9 (9.1)	95.1 (8.9)	95.1 (8.5)
Fasting plasma glucose, mmol/L	5.4 (0.5)	5.4 (0.5)	5.4 (0.5)	5.3 (0.5)	5.3 (0.5)
Current smoker, %	38.5	42.7	37.7	49.3	58.5
Current drinker, %	79.5	77.5	78.4	75.7	77.5
<b>Women in rural Japan (n = 4,852)</b>	<b>Sustained loss</b>	<b>Loss-gain</b>	<b>Stable</b>	<b>Gain-loss</b>	<b>Sustained gain</b>
Age, years	54.9 (9.0)	52.8 (8.6)	53.1 (9.2)	50.7 (9.2)	48.2 (9.9)
Weight, kg	54.0 (8.1)	53.6 (7.5)	52.9 (6.9)	51.6 (7.6)	52.6 (7.8)
Height, cm	154.1 (5.6)	154.8 (5.8)	154.6 (5.4)	155.3 (5.5)	155.7 (5.6)
Body mass index, kg/m <sup>2</sup>	22.7 (3.1)	22.4 (2.8)	22.1 (2.8)	22.8 (2.9)	21.7 (3.0)
HbA1c, %	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.2 (0.3)
HbA1c, mmol/mol	34.9 (3.7)	34.6 (3.4)	34.6 (3.6)	34.0 (3.4)	33.6 (3.3)

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Fasting plasma glucose, mg/dL	94.1 (9.1)	93.0 (8.3)	93.7 (8.8)	94.0 (8.0)	91.9 (7.9)
Fasting plasma glucose, mmol/L	5.2 (0.5)	5.2 (0.5)	5.2 (0.5)	5.2 (0.4)	5.1 (0.4)
Current smoker, %	5.5	8.1	6.6	8.5	11.5
Current drinker, %	24.2	27.2	26.5	27.1	30.9

The data are presented as the mean (SD) or %.

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## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Line 1–2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Line 23–41
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	Line 54–70
Objectives	3	State specific objectives, including any prespecified hypotheses	5	Line 70–71
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	6	Line 76–77
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	Line 77–92
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6	Line 86–91
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Line 92–94
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6–7	Line 99–119
Bias	9	Describe any efforts to address potential sources of bias	5	Line 79–86
Study size	10	Explain how the study size was arrived at	8	Line 138–139, 144–145

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Line 115–119
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7–8	Line 122–131
		(b) Describe any methods used to examine subgroups and interactions	8	Line 128–131
		(c) Explain how missing data were addressed	6	Line 88–89
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		NA
		(e) Describe any sensitivity analyses	8	Line 128–131
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Line 138–139, 144–145
		(b) Give reasons for non-participation at each stage	6	Line 90–91
		(c) Consider use of a flow diagram		NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9	Table 1
		(b) Indicate number of participants with missing data for each variable of interest		NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	10	Line 155–171
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	11–14	Tables 2 and 3
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11–14	Tables 2 and 3
		(b) Report category boundaries when continuous variables were categorized	11–15 (BMI)	Tables 2–4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		NA

Continued on next page Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14–15	Table 4
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	16	Line 205–213
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19	Line 256–284
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20–21	Line 313–322
Generalisability	21	Discuss the generalisability (external validity) of the study results	20	Line 299–312
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	Line 339–342

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Weight cycling and the subsequent onset of type 2 diabetes mellitus: 10-year cohort studies in urban and rural Japan

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014684.R3
Article Type:	Research
Date Submitted by the Author:	15-Mar-2017
Complete List of Authors:	Yokomichi, Hiroshi; University of Yamanashi, Department of Health Sciences Ohde, Sachiko; St. Luke's International University, Center for Clinical Epidemiology Takahashi, Osamu; St. Luke's International University, Center for Clinical Epidemiology Mochizuki, Mie; University of Yamanashi, Department of Pediatrics Takahashi, Atsunori; University of Yamanashi, Department of Health Sciences Yoda, Yoshioki; Yamanashi Koseiren Health Care Center Tsuji, Masahiro; Yamanashi Koseiren Health Care Center Akiyama, Yuka; University of Yamanashi, Department of Health Sciences Yamagata, Zentaro; The University of Yamanashi, Interdisciplinary Graduate School of Medicine and Engineering
<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Diabetes and endocrinology, Health services research, Nutrition and metabolism, Sports and exercise medicine
Keywords:	body weight changes, type 2 diabetes, body mass index, Asian, sarcopenia

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Manuscripts

1 Yokomichi H et al.

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3 1 **Weight cycling and the subsequent onset of type 2 diabetes mellitus:**  
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5 2 **10-year cohort studies in urban and rural Japan**

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8 3 Hiroshi Yokomichi<sup>1\*</sup>, Sachiko Ohde<sup>2</sup>, Osamu Takahashi<sup>2</sup>, Mie Mochizuki<sup>3</sup>, Atsunori  
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10 4 Takahashi<sup>1</sup>, Yoshioki Yoda<sup>4</sup>, Masahiro Tsuji<sup>4</sup>, Yuka Akiyama<sup>1</sup> and Zentaro Yamagata<sup>1</sup>

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39 17 **Keywords:** body weight changes; type 2 diabetes; body mass index; Asian; sarcopenia

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3 **ABSTRACT**

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6 **Objective:** To investigate how weight cycling (gaining and losing weight) affects the risk of  
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9 diabetes.

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12 **Design:** Cohort studies.

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15 **Setting:** Primary healthcare in urban and rural Japan.

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18 **Participants:** 20,708 urban and 9,670 rural residents.

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22 **Primary outcome measures:** Odds ratios (ORs) for diabetes in those with weight loss,  
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24 weight loss-gain, stable weight, weight gain-loss and weight gain over 10 years. Weight gain  
25  
26 and loss were defined as a change of more than  $\pm 4\%$  from baseline weight.  
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31 **Results:** In the urban region, the ORs relative to the stable group for the loss-gain and  
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33 gain-loss groups were 0.63 (95% CI: 0.45–0.89) and 0.51 (95% CI: 0.32–0.82) for men and  
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35 0.72 (95% CI: 0.39–1.34) and 1.05 (95% CI: 0.57–1.95) for women. In the rural region, they  
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37 were 1.58 (95% CI: 0.78–3.17) and 0.44 (95% CI: 0.15–1.29) in men and 0.41 (95% CI:  
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39 0.12–1.44) and 0.77 (95% CI: 0.28–2.14) in women. The ORs for an increase in weight  
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41 between 5 and 10 kg from the age of 20 years were 1.54 (95% CI: 1.03–2.30) in men and  
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43 0.96 (95% CI: 0.55–1.65) in women.  
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46 **Conclusions:** In Japan, weight cycling was associated with a significant reduction in the risk  
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48 of diabetes for men from urban regions. The associations were unclear for women from urban  
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50 regions and both men and women from rural regions. These results differ from those in  
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52 Western studies, probably because of differences in diet, insulin secretion and sensitivity and  
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54 weight-consciousness.  
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3 45 **Strengths and limitations of this study**  
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- 6 ● Participants were invited from both urban and rural Japan.  
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8 ● Several weight change patterns, including weight gain after loss and loss after gain, were  
9 measured.  
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11 ● Odds ratios may change with weight changes of more than  $\pm 4\%$  in 10 years.  
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13 ● The levels of insulin secretion and sensitivity were not measured.  
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15 ● Whether participants' weight loss was intentional was undetermined.  
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53 **INTRODUCTION**

54 Weight gain is a well-known risk factor for incidental type 2 diabetes. Research involving  
55 people of Western, Oriental and African descent has quantitatively established the risks of  
56 developing diabetes linked to weight gain.<sup>1-3</sup> Researchers have also raised the question of  
57 whether repeatedly gaining and losing weight (weight cycling) is an independent risk factor  
58 for developing diabetes. Studies on this topic have reported inconsistent results in Westerners  
59 in Europe and North America. Several prospective studies suggest that weight cycling is a  
60 risk factor for type 2 diabetes, but others do not.<sup>4-8</sup> To our knowledge, the risk of diabetes in  
61 Asian weight cyclers has not been researched.

62 There is a preconception linking being slim to an aesthetic standard,<sup>9 10</sup> and many Asian  
63 women therefore try to lose weight.<sup>11 12</sup> Another group likely to try to reduce their weight is  
64 middle-aged Asian businesspeople with few opportunities for physical activity. Recent  
65 studies have demonstrated that East Asians are much more likely than Westerners to develop  
66 type 2 diabetes at a lower body mass index (BMI).<sup>13</sup> It may therefore take only a small  
67 change in weight to alter the risk of diabetes for this group. The literature indicates that in  
68 Japan, diet, physical activity, prevalence of overweight individuals and aesthetic  
69 consciousness are different among urban and rural residents.<sup>14 15</sup> The aim of this study was to  
70 establish whether weight cyclers in Japan were at an increased risk of diabetes. We used  
71 Japanese urban and rural data to examine this question in populations with varying lifestyles.

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3 **77 METHODS**

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5 **78 Study participants and measurements**

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79 These cohort studies involved participants from both an urban area, Tokyo and a rural area,  
80 Yamanashi Prefecture. In Tokyo, participants were employees of private companies who  
81 underwent medical check-ups between January 2005 and December 2014 at St. Luke's  
82 International Hospital. These annual check-ups were based on a legal obligation imposed by  
83 the Industrial Safety and Health Act in Japan.<sup>16</sup> In Yamanashi Prefecture, participants were  
84 employees and also residents who paid for a private comprehensive medical check-up  
85 between April 1999 and March 2009 at the Yamanashi Koseiren Health Care Center. A subset  
86 of participants in Yamanashi used a subsidy from their employers or administrative agencies  
87 for this check-up. Those from the urban area therefore received approximately annual  
88 medical check-ups over a 10-year period, and those in the rural area received occasional  
89 voluntary check-ups. Participants were included in the analysis if they had no diagnosis of  
90 diabetes and an HbA1c less than 6.5% (48 mmol/mol) during a baseline period of the first  
91 three years of the 10-year period. If they attended two or three medical check-ups in the first  
92 three years, the data from the first visit were used as the baseline. Participants were also  
93 required to attend at least two medical check-ups during the last 7 years of the study. They  
94 therefore received three to eight medical check-ups over the period, to enable us to categorise  
95 weight change patterns (exposure). The onset of diabetes was indicated by the results of  
96 questions about the diagnosis of diabetes, the commencement of diabetic therapies or  
97 glycated haemoglobin (HbA1c)  $\geq 6.5\%$  (48 mmol/mol).<sup>17 18</sup> In Tokyo, trained nurses  
98 interviewed participants over 20 years old to establish changes in weight. BMI was calculated  
99 as the participant's weight in kilograms divided by the square of their height in metres.

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101 **Weight change categories**

102 The participants were categorised into five groups by their pattern of weight change during  
103 the 3–10 years after the baseline (Figure 1). The stable group included all participants whose  
104 weight did not change by more than  $\pm 4\%$  from the baseline. The sustained gain group  
105 consisted of those who gained more than 4% of their baseline weight and did not  
106 subsequently lose it again. The sustained loss group included those who lost more than 4% of  
107 their baseline weight and did not subsequently regain it. The gain-loss group included all  
108 participants who gained more than 4% of their baseline weight, but later brought their weight  
109 back below +4%. The loss-gain group included participants who lost more than 4% of their  
110 baseline weight but brought their weight back above  $-4\%$ . When the participants had been  
111 categorised, we measured whether they developed diabetes. The length of time over which  
112 the participants were observed to see if they developed diabetes was between 1 and 6 years.  
113 Any data measured after a diagnosis of diabetes were ignored to conserve the temporality of  
114 exposure to outcome for epidemiological causation.<sup>19</sup>

115 The  $\pm 4\%$  change in weight used for this categorisation was considered to be approximately  
116 a one-unit change for a person with a BMI of 22 kg/m<sup>2</sup>. This was based on the 2014 reference  
117 mean BMIs for Japanese men and women of 23.6 kg/m<sup>2</sup> and 21.7 kg/m<sup>2</sup>.<sup>20</sup> The gain-loss and  
118 loss-gain groups were the weight cyclers of interest in this study.

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120 **Statistical analysis**

121 The baseline characteristics recorded for the participants included age, weight, height, BMI,  
122 HbA1c and fasting plasma glucose. We used univariate and multivariable logistic regressions  
123 to compare the risk of diabetes between the groups. In the data from the urban group, the

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3 124 covariates used for the adjustment at baseline were age, weight change from the age of 20,  
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5 125 BMI, smoking habits, alcohol consumption and physical activity. In the data from the rural  
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7 126 group, the available covariates for the adjustment at baseline were age, BMI, smoking habits  
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10 127 and alcohol consumption. Means of follow-up duration and numbers of measurements for  
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12 128 each weight change pattern group were calculated. The analyses were stratified by sex.  
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14 129 Another focus of this study was the impact of weight cycling on incidental diabetes in  
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16 130 middle-aged individuals. For a sensitivity analysis, we therefore restricted the analyses to a  
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18 131 population aged 45 to 64 years old. All statistical analyses used SAS statistical software  
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20 132 (version 9.3, SAS Institute, NC, USA). The descriptive statistics were reported as the means  
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22 133 and standard deviations (SD). All reported p-values were two-sided; p-values of < 0.05 were  
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24 134 considered statistically significant.  
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## 136 RESULTS

### 137 Participants

138 In total, 10,094 men and 10,614 women were enrolled from the Tokyo urban area, and 4,818  
139 men and 4,852 women from Yamanashi Prefecture. Their baseline characteristics are shown  
140 in Table 1 and Supplementary.

141 **Table 1. Baseline characteristics of the participants from urban (Tokyo) and rural**  
142 **(Yamanashi Prefecture) regions of Japan**

Characteristics, mean (standard deviation)	Men	Women
<b>Urban region</b>		
No.	10,094	10,614
Age, years	49.6 (11.9)	48.3 (11.3)
Weight, kg	68.8 (9.7)	52.3 (7.4)

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Height, cm	170.4 (6.1)	157.7 (5.6)
Body mass index, kg/m <sup>2</sup>	23.7 (2.8)	21.0 (2.9)
HbA1c, %	5.4 (0.3)	5.3 (0.4)
(HbA1c, mmol/mol)	35.3 (3.7)	35.0 (3.8)
Fasting plasma glucose, mg/dL	100.8 (8.6)	94.5 (8.0)
(Fasting plasma glucose, mmol/L)	5.6 (0.5)	5.2 (0.4)

#### Rural region

No.	4,818	4,852
Age, years	51.2 (10.3)	52.1 (9.4)
Weight, kg	65.7 (9.1)	53.1 (7.5)
Height, cm	168.1 (6.2)	154.8 (5.6)
Body mass index, kg/m <sup>2</sup>	23.2 (2.7)	22.1 (2.9)
HbA1c, %	5.3 (0.3)	5.3 (0.3)
(HbA1c, mmol/mol)	34.3 (3.8)	34.4 (3.5)
Fasting plasma glucose, mg/dL	96.3 (9.0)	93.2 (8.5)
(Fasting plasma glucose, mmol/L)	5.3 (0.5)	5.2 (0.5)

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#### 144 Risk of diabetes in urban and rural Japan

145 Table 2 shows means (SDs) of follow-up duration and numbers of measurements in each  
 146 weight change group. The numbers of measurements were smallest in the stable group in  
 147 both sexes and both regions. Tables 3 and 4 show the incidence of diabetes and the odds  
 148 ratios (ORs) for each explanatory variable in the urban and rural regions.

149

#### 150 Table 2. Means (standard deviations) of follow-up duration and numbers of 151 measurements in the groups of weight change patterns

Urban region	Weight change pattern over 10	Follow-up duration,	No. of measurements
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	years	years	
Men	Sustained loss	7.7 (1.9)	5.8 (1.6)
	Loss-gain	8.2 (1.2)	5.8 (1.4)
	Stable	7.9 (1.7)	4.9 (1.7)
	Gain-loss	8.2 (1.2)	5.7 (1.4)
	Sustained gain	7.4 (1.9)	5.4 (1.6)
Women	Sustained loss	7.9 (1.7)	6.0 (1.5)
	Loss-gain	8.2 (1.2)	5.9 (1.4)
	Stable	7.9 (1.6)	5.0 (1.7)
	Gain-loss	8.2 (1.1)	5.9 (1.4)
	Sustained gain	7.5 (1.9)	5.6 (1.6)
Rural region	Weight change pattern over 10 years	Follow-up duration	No. of measurements
Men	Sustained loss	7.3 (1.7)	5.2 (1.6)
	Loss-gain	7.9 (1.4)	6.2 (1.2)
	Stable	7.1 (1.9)	5.2 (1.6)
	Gain-loss	7.8 (1.4)	6.1 (1.3)
	Sustained gain	7.4 (1.6)	5.4 (1.6)
Women	Sustained loss	7.4 (1.7)	5.4 (1.5)
	Loss-gain	7.9 (1.3)	6.1 (1.3)
	Stable	7.0 (1.8)	5.0 (1.6)
	Gain-loss	7.9 (1.4)	6.0 (1.3)
	Sustained gain	7.3 (1.6)	5.1 (1.6)

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153 **Table 3. The incidence and odds ratios (95% CIs) of diabetes for different patterns of**  
 154 **weight change over 10 years among urban residents in Japan**

Exposure variables	Acquired DM / No. of subjects (incidence, %)	Crude	Multivariate
<b>Men (no. for multivariate analysis = 10,094)</b>			
Baseline age	Per 10 years	—	1.44 (1.33–1.55)
Weight change	< -5	7/1438 (0.5)	2.18 (1.14–4.18)

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from 20 years of age, kg	-5 to +5	73/10646 (0.7)	Ref	Ref
	+5 to +10	31/3200 (1.0)	1.98 (1.45–2.72)	1.54 (1.03–2.30)
	> +10	78/2166 (3.6)	3.37 (2.54–4.48)	2.08 (1.40–3.10)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	6/387 (1.6)	1.35 (0.57–3.16)	0.88 (0.29–2.70)
	18.5–22	49/4236 (1.2)	Ref	Ref
	22–25	168/7220 (2.3)	2.04 (1.48–2.89)	1.73 (1.14–2.63)
	> 25	190/4699 (4.0)	3.60 (2.62–4.94)	2.52 (1.60–3.95)
Weight change pattern over 10 years	Sustained loss	66/1903 (3.5)	1.39 (1.03–1.87)	1.11 (0.77–1.59)
	Loss–gain	87/4644 (1.9)	0.74 (0.56–0.97)	0.63 (0.45–0.89)
	Stable	142/5621 (2.5)	Ref	Ref
	Gain–loss	38/3063 (1.2)	0.49 (0.34–0.70)	0.51 (0.32–0.82)
	Sustained gain	80/1311 (6.1)	2.51 (1.89–3.32)	3.07 (2.15–4.39)
Smoking	None	123/6385 (1.9)	Ref	Ref
	Ex-smoker	150/5940 (2.5)	1.32 (1.04–1.68)	0.97 (0.71–1.31)
	Current smoker	140/4217 (3.3)	1.75 (1.37–2.23)	1.73 (1.25–2.34)
Alcohol drinking	None	69/2250 (3.1)	Ref	Ref
	Sometimes	48/1667 (2.9)	0.94 (0.65–1.36)	0.96 (0.66–1.40)
	Usually	156/6177 (2.5)	0.82 (0.61–1.09)	0.78 (0.58–1.05)
Amount of walking per day	Per 30 min	—	0.996 (0.92–1.08)	1.01 (0.92–1.11)
	0–1	85/3282 (2.6)	Ref	Ref
Physical activity (sessions/week)	1–2	108/4105 (2.6)	1.02 (0.76–1.36)	1.02 (0.76–1.36)
	3–5	43/1541 (2.8)	1.08 (0.74–1.57)	0.98 (0.67–1.45)
	6–7	37/1166 (3.2)	1.23 (0.83–1.82)	1.06 (0.69–1.62)
<b>Women (no. for multivariate analysis = 10,614)</b>				
Baseline age	Per 10 years	—	1.66 (1.48–1.87)	1.78 (1.50–2.12)
	< -5	11/439 (2.5)	0.71 (0.33–1.54)	0.48 (0.18–1.25)
Weight change from 20 years of age, kg	-5 to +5	61/5243 (1.2)	Ref	Ref
	+5 to +10	109/4779 (2.3)	1.42 (0.93–2.16)	0.96 (0.55–1.65)
	> +10	232/6081 (3.8)	5.41 (3.92–7.47)	2.10 (1.20–3.67)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	20/2916 (0.7)	1.24 (0.74–2.08)	1.47 (0.76–2.86)
	18.5–22	52/9388 (0.6)	Ref	Ref
	22–25	60/3676 (1.6)	2.98 (2.05–4.33)	2.01 (1.21–3.34)

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	> 25	57/1470 (3.9)	7.24 (4.95–10.59)	2.91 (1.53–5.52)
Weight change pattern over 10 years	Sustained loss	24/1661 (1.4)	2.11 (1.25–3.54)	1.48 (0.80–2.74)
	Loss–gain	32/4022 (0.7)	1.15 (0.72–1.86)	0.72 (0.39–1.34)
	Stable	36/5212 (1.3)	Ref	Ref
	Gain–loss	30/4630 (0.6)	0.94 (0.58–1.53)	1.05 (0.57–1.95)
	Sustained gain	67/1925 (3.5)	5.19 (3.45–7.80)	7.00 (4.11–11.94)
Smoking	None	156/14,194 (1.1)	Ref	Ref
	Ex-smoker	17/1789 (1.0)	0.86 (0.52–1.143)	0.85 (0.45–1.61)
	Current smoker	16/1467 (1.1)	0.99 (0.59–1.67)	1.20 (0.63–2.32)
Alcohol drinking	None	78/5669 (1.4)	Ref	Ref
	Sometimes	20/2035 (1.0)	0.71 (0.43–1.17)	0.91 (0.55–1.52)
	Usually	27/2910 (0.9)	0.67 (0.43–1.04)	0.95 (0.60–1.51)
Amount of walking per day	Per 30 min	—	1.01 (0.93–1.11)	1.01 (0.90–1.13)
	0–1	37/3894 (1.0)	Ref	Ref
Physical activity (sessions/week)	1–2	42/3760 (1.1)	1.18 (0.76–1.84)	1.11 (0.70–1.75)
	3–5	27/1874 (1.4)	1.52 (0.93–2.52)	1.14 (0.67–1.94)
	6–7	19/1086 (1.7)	1.86 (1.06–3.24)	1.43 (0.79–2.60)

155 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

156 **Table 4. The incidence and odds ratios (95% CIs) of diabetes for different patterns of**  
 157 **weight change over 10 years among rural residents in Japan**

Exposure variables		Acquired DM / No. of subjects (incidence, %)	Crude	Multivariate
<b>Men (no. for multivariate analysis = 4,818)</b>				
Baseline age	Per 10 years	—	1.36 (1.08–1.72)	1.60 (1.24–2.05)
	< 18.5	0/167 (0)	—	—
Baseline BMI, kg/m <sup>2</sup>	18.5–22	10/1425 (0.7)	Ref	Ref
	22–25	21/2079 (1.0)	1.44 (0.68–3.08)	1.69 (0.79–3.63)
	> 25	35/1148 (3.1)	4.45 (2.19–9.03)	5.81 (2.82–11.97)

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	Sustained loss	4/725 (0.6)	0.43 (0.15–1.25)	0.36 (0.12–1.05)
Weight change pattern over 10 years	Loss–gain	13/681 (1.9)	1.50 (0.75–3.00)	1.58 (0.78–3.17)
	Stable	22/1719 (1.3)	Ref	Ref
	Gain–loss	4/916 (0.4)	0.34 (0.12–0.99)	0.44 (0.15–1.29)
	Sustained gain	23/778 (3.0)	2.35 (1.30–4.24)	3.15 (1.70–5.83)
Smoking	None	23/1695 (1.4)	Ref	Ref
	Ex-smoker	8/998 (0.8)	0.59 (0.26–1.32)	0.72 (0.32–1.64)
	Current smoker	35/2126 (1.7)	1.22 (0.72–2.07)	1.50 (0.85–2.62)
Drinking	None	11/1071 (1.0)	Ref	Ref
	Drinker	55/3748 (1.5)	1.44 (0.75–2.75)	1.52 (0.79–2.94)
<b>Women (no. for multivariate analysis = 4,852)</b>				
Baseline age	Per 10 years	—	1.43 (0.99–2.06)	1.23 (0.83–1.84)
Baseline BMI, kg/m <sup>2</sup>	< 18.5	0/411 (0)	—	—
	18.5–22	7/2135 (0.3)	Ref	Ref
	22–25	14/1563 (0.9)	2.75 (1.11–6.82)	2.69 (1.07–6.75)
	> 25	13/744 (1.8)	5.41 (2.15–13.60)	5.29 (2.07–13.51)
Weight change pattern over 10 years	Sustained loss	3/863 (0.3)	0.37 (0.11–1.29)	0.32 (0.09–1.10)
	Loss–gain	3/757 (0.4)	0.42 (0.12–1.47)	0.41 (0.12–1.44)
	Stable	15/1615 (0.9)	Ref	Ref
	Gain–loss	5/827 (0.6)	0.65 (0.24–1.79)	0.77 (0.28–2.14)
	Sustained gain	8/791 (1.0)	1.09 (0.46–2.58)	1.43 (0.59–3.48)
Smoking	None	2/646 (0.3)	Ref	Ref
	Ex-smoker	29/3822 (0.8)	2.45 (0.58–10.31)	2.19 (0.52–9.26)
	Current smoker	3/375 (0.8)	2.60 (0.43–15.60)	3.33 (0.55–20.28)
Drinking	None	31/3542 (0.9)	Ref	Ref
	Drinker	3/1311 (0.2)	0.26 (0.08–0.85)	0.29 (0.09–0.95)

158 DM, diabetes mellitus; CI, confidence interval; Ref, reference group; BMI, body mass index

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160 Table 5 shows the risk of diabetes linked to weight cycling in the middle-aged population.

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**Table 5. The incidence and odds ratios of diabetes for different patterns of weight change over 10 years in middle-aged people (45–64 years) in Japan**

Exposure variables	Acquired DM / No. of subjects (incidence, %)	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)	
<b>Urban middle-aged men (no. for multivariate analysis = 4,882)</b>				
Weight change pattern over 10 years	Sustained loss	35/981 (3.6)	1.04 (0.65–1.67)	0.97 (0.60–1.55)
	Loss-gain	62/2203 (2.8)	0.79 (0.53–1.18)	0.74 (0.49–1.11)
	Stable	100/2749 (3.6)	Ref	Ref
	Gain-loss	26/1098 (2.4)	0.56 (0.32–0.999)	0.57 (0.32–1.01)
	Sustained gain	50/489 (10.2)	3.09 (2.00–4.76)	3.13 (2.00–4.89)
<b>Urban middle-aged women (no. for multivariate analysis = 5,053)</b>				
Weight change pattern over 10 years	Sustained loss	15/994 (1.5)	1.30 (0.62–2.73)	1.13 (0.53–2.41)
	Loss-gain	20/1992 (1.0)	0.87 (0.43–1.77)	0.76 (0.37–1.57)
	Stable	24/2285 (1.1)	Ref	Ref
	Gain-loss	17/1642 (1.0)	0.74 (0.34–1.62)	0.80 (0.36–1.77)
	Sustained gain	40/603 (6.6)	5.62 (3.05–10.37)	6.97 (3.67–13.25)
<b>Rural middle-aged men (no. for multivariate analysis = 2,937)</b>				
Weight change pattern over 10 years	Sustained loss	3/447 (0.7)	0.48 (0.14–1.66)	0.42 (0.12–1.47)
	Loss-gain	11/449 (2.5)	1.78 (0.81–3.91)	1.76 (0.80–3.87)
	Stable	15/1078 (1.4)	Ref	Ref
	Gain-loss	4/546 (0.7)	0.52 (0.17–1.58)	0.58 (0.19–1.77)
	Sustained gain	12/417 (2.9)	2.10 (0.98–4.53)	2.48 (1.12–5.49)
<b>Rural middle-aged women (no. for multivariate analysis = 3,347)</b>				
Weight change pattern over 10 years	Sustained loss	1/638 (0.2)	0.16 (0.02–1.25)	0.14 (0.02–1.01)
	Loss-gain	3/579 (0.5)	0.54 (0.15–1.92)	0.54 (0.15–1.94)
	Stable	11/1140 (1.0)	Ref	Ref
	Gain-loss	4/558 (0.7)	0.74 (0.24–2.34)	0.82 (0.26–2.62)
	Sustained gain	5/432 (1.2)	1.20 (0.42–3.48)	1.30 (0.44–3.84)

Multivariable logistic regression-calculated odds ratios with an adjustment for baseline age and BMI, weight change from 20 years of age, smoking and drinking habits, amount of walking per day and sessions of physical activity per week in the urban data, and baseline age, BMI and smoking and drinking habits in the rural data.

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169 **DISCUSSION**

170 The data for the Japanese urban region suggest that the risk of diabetes in male weight  
171 cyclers was significantly lower than in those who maintained a stable weight (Table 3).  
172 The diabetes risk for female weight cyclers in the urban region was non-significantly  
173 lower than or similar to the risk for those maintaining a stable weight. The data for the  
174 rural region suggest no difference in diabetes risk for weight-cycling men and a  
175 non-significantly lower risk for women compared with maintaining a stable weight  
176 (Table 4). These results are reinforced by a sensitivity analysis focusing on middle-aged  
177 individuals, yielding almost identical non-significant ORs (Table 5).

178 These observations are not consistent with those from previous studies of Western  
179 populations.<sup>4-6,21</sup> These studies showed that weight cycling significantly or  
180 non-significantly increased the risk of diabetes for point estimates. In the Framingham  
181 Heart Study, approximately 1 kg/m<sup>2</sup> of weight cycling in middle-aged Americans  
182 carried a hazard ratio of 1.1 (95% CI: 0.8–1.5) for the risk of diabetes after adjusting for  
183 sex and BMI at 25 years of age.<sup>4</sup> In American middle-aged women examined in the  
184 National Health and Nutrition Examination Survey, weight cycling of 4.5–9.1 kg and  
185 9.1–22.2 kg with intentional weight loss three or more times in 4 years carried ORs for  
186 the risk of diabetes of 1.11 (95% CI: 0.89–1.37) and 1.39 (95% CI: 0.90–2.13).<sup>5</sup> A study  
187 from a cohort of medical students at the Johns Hopkins University School of Medicine  
188 reported that the highest quartile of BMI variability for ages between 25 and 45 years  
189 had an OR of 2.1 (95% CI: 1.0–4.6) for the risk of diabetes after 50 years, compared  
190 with the other three quartiles.<sup>21</sup> In a large German cohort, weight cycling of  $\geq 1.5$   
191 kg/year was significantly associated with an adjusted hazard ratio of 1.34.<sup>6</sup>

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5 192 The disparity between the results of this study and the Western studies may be  
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7 193 because of ethnic differences in diet,<sup>22</sup> the capacity to gain weight<sup>23</sup> and  
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9 194 self-consciousness about body weight.<sup>24</sup> Further research is needed to explore why the  
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11 195 relationship between weight cycling and risk of diabetes is reversed for Western and  
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13 196 East Asian populations. It may be attributable to different motivations to lose weight  
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15 197 because of different cultural views on dieting and body self-consciousness.<sup>25</sup> Those East  
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17 198 Asians who try to lose weight may be more concerned about the poor health outcomes  
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19 199 of being overweight. The Westerners in the studies who tried to lose weight may have  
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21 200 been more likely to lose and regain a great deal of weight, and therefore potentially ran  
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23 201 the risk of poor health outcomes.

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28 202 The urban data in this study showed that an increase of more than +5 kg above  
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30 203 weight at 20 years old increased the risk of developing diabetes with a dose–response  
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32 204 relationship in both men and women (Table 3). An increase of more than +10 kg from  
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34 205 weight at 20 years old more than doubled the risk of diabetes compared with  
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36 206 maintaining weight within  $\pm 5$  kg. These results agree with the study involving a US  
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38 207 cohort, which reported a relative risk of 3.2 (95% CI: 1.4–7.4) for the highest quartile of  
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40 208 an increase in BMI from 25 to 45 years of age in comparison with the other three  
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42 209 quartiles.<sup>21</sup> A dose–response relationship of weight change from that at 20 years old to  
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44 210 the risk of diabetes was seen in urban Japanese women, with ORs of 0.48 (95% CI:  
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46 211 0.18–1.25) for a change of less than 5 kg, 0.96 (95% CI: 0.55–1.65) for an increase of  
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48 212 between 5 and 10 kg and 2.10 (95% CI: 1.20–3.67) for an increase greater than 10 kg  
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50 213 (Table 3). In contrast, Japanese men who lost 5 kg or more of body weight between the  
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52 214 age of 20 years and early middle age had an OR of 1.68 (95% CI: 0.75–3.80). This



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5 215 paradoxically increased OR was probably because of the small number of participants  
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7 216 (seven) who developed diabetes among a weight loss group of 1,438 people.  
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10 217 This study had several limitations. The first of these was the threshold of  $\pm 4\%$  weight  
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12 218 change in 10 years. This was drawn from a study in the United Kingdom on the  
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14 219 association between weight change and the risk of diabetes.<sup>26</sup> It was calculated as  
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16 220 approximately one BMI unit in Japanese people with a mean BMI of  $23 \text{ kg/m}^2$ .  
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18 221 However, the threshold for categorisation of weight cycling is likely to vary by mean  
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20 222 BMI in different ethnicities, because of different insulin sensitivities.<sup>13 27</sup> Second, we  
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22 223 did not evaluate insulin sensitivity. Measuring fasting plasma glucose and insulin  
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24 224 concentration to calculate HOMA-IR,<sup>28</sup> an index of insulin resistance, would have  
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26 225 allowed us to assess the association between weight cycling and the physiological  
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28 226 hazard of diabetes. Third, the weight changes recorded in the rural region may have  
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30 227 been misclassified because of missing data from the years when participants did not  
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32 228 undergo a medical check-up. However, this misclassification would have biased the  
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34 229 ORs towards the null hypothesis, and we believe that this would therefore not change  
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36 230 the conclusions for the rural region. Fourth, we could not examine whether weight  
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38 231 cycling was intentional. We consider, however, that a subset of unintentional weight loss  
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40 232 could be attributed to metabolic diseases, and patients with such diseases would not  
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42 233 usually be able to regain the weight within a short time. Fifth, the follow-up duration  
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44 234 and the numbers of weight measurements varied among the weight change groups.  
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46 235 However, because perfect categorisation of weight changes over time would be  
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48 236 impossible, we think that our study design enables us to answer the study question.  
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50 237 Sixth, the urban data for weight at 20 years old were self-reported by participants. They  
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5 238 may therefore have been affected by recall bias. Seventh, a subset of the diagnoses in  
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7 239 this study were not made by physicians but via an epidemiological criteria.<sup>17</sup> However,  
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10 240 most observational studies rely on epidemiological criteria for detecting diabetes, and  
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12 241 the use of a consistent diagnostic criterion allows researchers to compare the risk of  
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14 242 diabetes onset between the reference group and groups of interest. Last, this study lacks  
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16 243 any information about lifestyle, including diet, marital status, job type and car  
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18 244 ownership. All these may partly explain the association between weight cycling and  
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20 245 diabetes.

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24 246 This study also has several strengths. First, to the best of our knowledge, it is the first  
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26 247 study to explore the relationship between weight cycling and the risk of diabetes in  
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28 248 Asians. The relationship found in this study was almost directly opposite to that found  
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30 249 in US studies, so further research in East Asians is necessary to confirm the findings.  
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32 250 Next, this study was conducted in two different populations (urban and rural residents).  
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34 251 The ORs of the risk of diabetes were 1.05 (95% CI: 0.57–1.95) in the urban women  
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36 252 with weight gain-loss (Table 3) and 1.58 (95% CI: 0.78–3.17) in rural men with weight  
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38 253 loss-gain (Table 4). All other weight-cycling patterns for both sexes in both urban and  
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40 254 rural regions were negatively correlated with the risk of diabetes, although some  
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42 255 relationships were not statistically significant (Tables 3 and 4). Third, the study included  
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44 256 a large number of participants across both sexes (approximately 10,000 in the urban  
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46 257 region and 5,000 in the rural region). Its findings are therefore likely to be generalisable  
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48 258 to Japanese and East Asian weight cyclers.

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54 259 This study could help public health practitioners and on-site clinical professionals  
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56 260 prevent diabetes in the general population. A sustained weight gain of more than 4%

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5 261 over 10 years in middle age (Table 5) and more than 5 kg of additional weight gain  
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7 262 since the age of 20 years (Table 3) may both carry an increased risk of diabetes for both  
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10 263 sexes. Middle-aged people can easily undergo such a small weight gain over the short-  
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12 264 or long-term, so even non-diabetic people within the normal BMI range should be  
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14 265 cautious about the risks resulting from small weight gains throughout their lifetime. An  
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16 266 interventional study indicated that weight loss ( $-1.8 \text{ kg/m}^2$  of BMI in a diet intervention  
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18 267 group and  $-3.3 \text{ kg/m}^2$  of BMI in a diet-and-exercise intervention group) improved  
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21 268 insulin sensitivity in Japanese patients with obesity and type 2 diabetes.<sup>29</sup> Improved  
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23 269 insulin sensitivity was also observed in Americans who maintained their weight with  
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25 270 treadmill-based exercise and no alteration in their diet.<sup>30</sup> Studies have also demonstrated  
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27 271 that building muscle through exercising without changing weight improves insulin  
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29 272 sensitivity.<sup>31</sup>

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33 273 While not statistically significant, two weight-cycling patterns were found to result in  
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35 274 an increased risk of diabetes (Tables 3 and 4). Better insulin sensitivity leads directly to  
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37 275 a decreased risk of diabetes, so these results may be because of differences in how the  
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39 276 participants lost or gained weight (i.e. whether they lost or gained fat or muscle mass).  
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42 277 Recent studies have indicated that sarcopenia, the loss of skeletal muscle alone or with  
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44 278 increased fat mass in ageing, is a leading cause of death in old age.<sup>32</sup> The results of our  
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46 279 study, in the context of previous studies, suggest that over both the short- and long-term,  
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48 280 people might reduce their risk of diabetes by losing fat and maintaining muscle mass.

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283 **CONCLUSIONS**

284 In urban men in Japan, weight cycling was associated with a significant reduction in the  
285 risk of diabetes. No clear association was seen in either urban women or in men and  
286 women living in the rural region. The results were different from those seen in Western  
287 countries and may be attributed to differences in diet, endocrinological capacity to gain  
288 weight and weight-consciousness. The risk of diabetes seems to increase linearly with  
289 weight gain from the age of 20 years in urban Japanese men and women. A study that  
290 includes the measurement of insulin sensitivity is necessary to confirm these results and  
291 to improve the understanding of the risks for East Asian weight cyclers.

292 **(2,718 words; limit of 4,000 words)**

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5 293 **Acknowledgments** We thank all participants in this study and staff at the St. Luke's  
6  
7 294 International Hospital and the Yamanashi Koseiren Health Care Center for their support,  
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9 295 which made this study possible.  
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12  
13 296 **Competing interests** None declared.  
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15  
16 297 **Funding** This work was supported by the Ministry of Education, Culture, Sports,  
17  
18 298 Science and Technology of Japan (MEXT) (KAKENHI grant number: JP15K08730 and  
19  
20 299 JP15K15221). The funder had no role in study design, analysis, decision to publish or  
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22 300 preparation of the manuscript.  
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26 301 **Contributors** ZY, YY, MT and OT: setting up the study and data collection. HY, ZY,  
27  
28 302 MM and AT: designing the study. HY and AT: data analysis. HY: writing and revising  
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30 303 the draft. ZY, SO, MM, YA and HY: development of the discussion section. All authors  
31  
32 304 read and approved the final manuscript.  
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36 305 **Ethics approval** The ethics committee of the School of Medicine, University of  
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38 306 Yamanashi approved this study (approval number: H27-1417).  
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42 307 **Data sharing statement** No additional data are available.  
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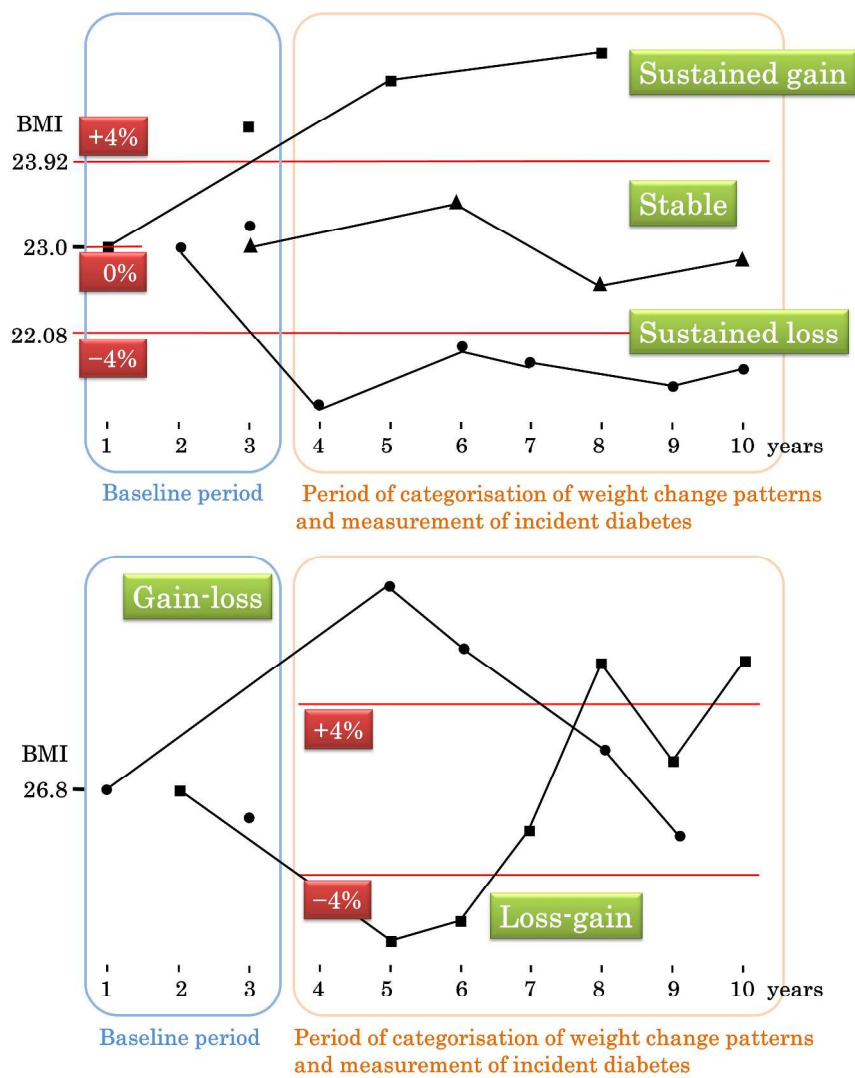
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5 396 **Figure 1. How participants were categorised into the five weight**  
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## Categorisation of weight change patterns



How participants were categorised into the five weight change patterns

Figure 1

339x454mm (300 x 300 DPI)

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**Supplementary. Baseline characteristics among groups of weight change patterns over 10 years**

<b>Men in urban Japan (n = 10,094)</b>	Sustained loss	Loss-gain	Stable	Gain-loss	Sustained gain
Age, years	52.3 (12.2)	51.2 (12.0)	50.3 (11.3)	46.0 (11.4)	44.9 (11.3)
Weight, kg	70.8 (10.4)	69.8 (9.5)	68.3 (9.0)	67.3 (9.5)	67.8 (10.8)
Height, cm	170.1 (6.2)	170.3 (6.1)	170.2 (6.0)	170.7 (6.1)	171.2 (6.1)
Body mass index, kg/m <sup>2</sup>	24.4 (3.0)	24.0 (2.7)	23.5 (2.6)	23.1 (2.8)	23.1 (3.2)
HbA1c, %	5.4 (0.4)	5.4 (0.3)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
HbA1c, mmol/mol	35.9 (3.9)	35.7 (3.7)	35.3 (3.7)	34.6 (3.7)	34.6 (3.4)
Fasting plasma glucose, mg/dL	102.3 (9.2)	101.5 (8.8)	101.0 (8.5)	99.0 (8.0)	99.8 (8.4)
Fasting plasma glucose, mmol/L	5.7 (0.5)	5.6 (0.5)	5.6 (0.5)	5.5 (0.4)	5.5 (0.5)
Weight change from 20 years of age, kg	+9.7 (9.1)	+9.0 (8.1)	+8.2 (7.9)	+7.0 (8.4)	+7.0 (20.5)
Current smoking, %	20.0	22.8	23.6	31.3	33.7
Usually drinking alcohol, %	61.7	62.3	63.8	57.3	55.2
Duration of walking per day, min	41.0 (38.3)	41.3 (41.7)	43.3 (41.5)	40.4 (35.2)	38.6 (36.0)
Physical activity of 6–7/week, %	11.2	12.0	11.9	10.4	11.6
<b>Women in urban Japan (n = 10,614)</b>	Sustained loss	Loss-gain	Stable	Gain-loss	Sustained gain
Age, years	52.4 (10.7)	51.1 (11.5)	48.9 (11.3)	45.7 (10.6)	43.5 (9.8)
Weight, kg	53.8 (8.0)	53.4 (7.8)	51.7 (7.0)	51.8 (7.1)	51.6 (7.4)
Height, cm	156.9 (5.7)	157.2 (5.9)	157.8 (5.6)	158.1 (5.5)	158.4 (5.3)
Body mass index, kg/m <sup>2</sup>	21.8 (3.0)	21.6 (3.0)	20.8 (2.7)	20.7 (2.7)	20.6 (2.8)
HbA1c, %	5.5 (0.4)	5.4 (0.4)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
HbA1c, mmol/mol	36.1 (4.1)	35.4 (3.8)	35.0 (3.8)	34.4 (3.6)	34.0 (3.7)
Fasting plasma glucose, mg/dL	96.5 (8.9)	95.7 (8.1)	94.6 (8.0)	93.2 (7.3)	92.8 (7.3)

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Fasting plasma glucose, mmol/L	5.4 (0.5)	5.3 (0.4)	5.3 (0.4)	5.2 (0.4)	5.2 (1.4)
Weight change from 20 years of age, kg	+4.1 (7.4)	+3.8 (7.3)	+2.4 (7.1)	+3.6 (7.1)	+2.2 (7.5)
Current smoking, %	6.6	6.7	5.7	9.9	11.8
Usually drinking alcohol, %	23.7	26.7	27.3	29.4	28.3
Duration of walking per day, min	42.9 (49.4)	41.2 (49.8)	42.3 (40.9)	41.5 (40.5)	43.8 (51.9)
Physical activity of 6–7/week, %	12.1	10.6	11.3	8.6	8.8
<b>Men in rural Japan (n = 4,818)</b>	<b>Sustained loss</b>	<b>Loss-gain</b>	<b>Stable</b>	<b>Gain-loss</b>	<b>Sustained gain</b>
Age, years	53.5 (10.3)	51.7 (9.8)	52.3 (10.1)	49.2 (10.1)	48.3 (10.5)
Weight, kg	67.2 (9.0)	66.2 (8.7)	66.0 (9.1)	64.7 (8.6)	64.3 (9.9)
Height, cm	167.5 (6.2)	168.0 (6.0)	167.8 (6.2)	168.5 (6.2)	168.8 (6.5)
Body mass index, kg/m <sup>2</sup>	23.9 (2.6)	23.4 (2.6)	23.4 (2.7)	22.8 (2.5)	22.5 (2.9)
HbA1c, %	5.3 (0.4)	5.3 (0.4)	5.3 (0.3)	5.2 (0.3)	5.2 (0.3)
HbA1c, mmol/mol	34.7 (3.9)	34.6 (3.9)	34.3 (3.7)	33.9 (3.8)	33.8 (3.5)
Fasting plasma glucose, mg/dL	97.5 (9.2)	96.4 (9.0)	96.9 (9.1)	95.1 (8.9)	95.1 (8.5)
Fasting plasma glucose, mmol/L	5.4 (0.5)	5.4 (0.5)	5.4 (0.5)	5.3 (0.5)	5.3 (0.5)
Current smoker, %	38.5	42.7	37.7	49.3	58.5
Current drinker, %	79.5	77.5	78.4	75.7	77.5
<b>Women in rural Japan (n = 4,852)</b>	<b>Sustained loss</b>	<b>Loss-gain</b>	<b>Stable</b>	<b>Gain-loss</b>	<b>Sustained gain</b>
Age, years	54.9 (9.0)	52.8 (8.6)	53.1 (9.2)	50.7 (9.2)	48.2 (9.9)
Weight, kg	54.0 (8.1)	53.6 (7.5)	52.9 (6.9)	51.6 (7.6)	52.6 (7.8)
Height, cm	154.1 (5.6)	154.8 (5.8)	154.6 (5.4)	155.3 (5.5)	155.7 (5.6)
Body mass index, kg/m <sup>2</sup>	22.7 (3.1)	22.4 (2.8)	22.1 (2.8)	22.8 (2.9)	21.7 (3.0)
HbA1c, %	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.3 (0.3)	5.2 (0.3)
HbA1c, mmol/mol	34.9 (3.7)	34.6 (3.4)	34.6 (3.6)	34.0 (3.4)	33.6 (3.3)

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Fasting plasma glucose, mg/dL	94.1 (9.1)	93.0 (8.3)	93.7 (8.8)	94.0 (8.0)	91.9 (7.9)
Fasting plasma glucose, mmol/L	5.2 (0.5)	5.2 (0.5)	5.2 (0.5)	5.2 (0.4)	5.1 (0.4)
Current smoker, %	5.5	8.1	6.6	8.5	11.5
Current drinker, %	24.2	27.2	26.5	27.1	30.9

The data are presented as the mean (SD) or %.

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## STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	Line 1–2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Line 23–42
<b>Introduction</b>				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5	Line 54–69
Objectives	3	State specific objectives, including any prespecified hypotheses	5	Line 69–71
<b>Methods</b>				
Study design	4	Present key elements of study design early in the paper	6	Line 79–80
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6	Line 79–89
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6	Line 80–89
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6	Line 93–97
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7	Line 102–110
Bias	9	Describe any efforts to address potential sources of bias	5	Line 82–89
Study size	10	Explain how the study size was arrived at	8	Line 138–139

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Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Line 115–117
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7–8	Line 121–128
		(b) Describe any methods used to examine subgroups and interactions	8	Line 129–131
		(c) Explain how missing data were addressed	6	Line 87–89, 92–95
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		NA
		(e) Describe any sensitivity analyses	8	Line 129–131
<b>Results</b>				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8	Line 138–139
		(b) Give reasons for non-participation at each stage	6	Line 89–95
		(c) Consider use of a flow diagram		NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8–9	Table 1
		(b) Indicate number of participants with missing data for each variable of interest		NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	9–10	Table 2
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10–13	Tables 3 and 4
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures		NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10–13	Tables 3 and 4
		(b) Report category boundaries when continuous variables were categorized	10–14 (BMI)	Tables 3–5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		NA



Continued on next page Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	14–15	Table 5
<b>Discussion</b>				
Key results	18	Summarise key results with reference to study objectives	16	Line 170–177
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18–19	Line 217–245
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19–20	Line 259–272
Generalisability	21	Discuss the generalisability (external validity) of the study results	19	Line 255–258
<b>Other information</b>				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	22	Line 297–300

\*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).